Clinical effects of Chinese herbal medicine for allergic rhinitis: Reviews of classical and modern literature

A thesis submitted in fulfilment of the requirements for the degree of Master of Science

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Declaration

I certify that except where due acknowledgement has been made, the work is that of the author alone; the work has not been submitted previously, in whole or in part, to qualify for any academic award; the content of the thesis is the result of work which has been carried out since the official commencement date of the approved research program; and any editorial work, paid or unpaid, carried out by a third party is acknowledged.

Jenny Kreiner

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Acronyms and abbreviations

ALT	Alanine transaminase
AR	Allergic rhinitis
ARIA	Allergic Rhinitis and its impact on Asthma
ASD	Asian sand storm
AS-IV	Astragaloside IV
AST	Aspartate aminotransferase
ATR	Atractyloside
BUN	Blood urea nitrogen
C	Cimifugin
CAMT	Camptothecin
CAM	Complementary and alternative medicine
cAMP	3′5′-cyclic adenosine monophosphate
CATR	Carboxytractyloside
CCL	Chemokine ligands
CD	Cluster of differentiation
CHM	Chinese herbal medicine
CM	Chinese medicine
COX	Cyclooxygenase
Cr	Creatinine
CREB	cAMP response element binding
cysLTs	Cysteinyl leukotrienes
Cϵ	Heavy chain
ECP	Eosinophil cationic protein
ECRHS	European Community Respiratory Health Study

EGFR	Epidermal growth factor receptor
ENT	Ear, nose and throat
ERKs	Extracellular signal-regulated kinases
FcεRI	*Fc* receptor specific for ε heavy chains
GC	Prim-*O*-glucosylcimifugin
GH	sec-*O*-glucosylhamaudol
Glu	Glucocorticosteroids
GM-CSF	Colony-stimulating factor
GV	4′-*O*-β-D-glucosyl-5-*O*-methylvisamminol
HCA	Hierarchical cluster analysis
IAR	Intermittent allergic rhinitis
ICAM-1	Intracellular adhesion molecule 1
IgE	Immunoglobulin E
IL	Interleukin
iNOS	Inducible nitric oxide synthase
IRF-3	Interferon regulatory factor-3
ITAMs	Immune-receptor tyrosine-based activation motifs
ITT	Intention to treat
Iϵ	Light chain
JNK	c-Jun NH (2) terminal kinase
LOX	5-lipoxygenase
LT	Leukotriene
MAPKs	Mitogen activated protein kinases
MD	Mean difference
MDA	Malondialdehyde
MEG	Methyleugenol

MHC	Major histocompatibility complex
mRNA	Messenger ribonucleic acid
MV	5-*O*-methylvisamminol
NAC	Nasal allergen challenge
NFAT	Nuclear factor of activator T-cells
NF-κβ	Nuclear factor kappa beta
NO	Nitric oxide
Nrf2	Nuclear factor erythroid 2
OTC	Over-the-counter
OVA	Ovalbumin
PAR	Perennial allergic rhinitis
PC	Principal component
PCA	Principal component analysis
PER	Persistent allergic rhinitis
PGD_2	Prostaglandin D_2
PGE_2	Prostaglandin E_2
PMN	Polymorphonuclear neutrophils
PMs	Particulate matters
PPAR-γ	Peroxisome proliferation-activated receptor-γ
PSVN	Plant specimen voucher number
PTX	Paclitaxel
RAST	Radioallergosorbent test
RCTs	Randomised controlled trials
RNA	Ribonucleic acid
ROS	Reactive oxidative species
RQLQ	Rhinoconjunctivitis Quality of Life Questionnaire

RR	Relative risk
SAR	Seasonal allergic rhinitis
SCIT	Subcutaneous immunotherapy
SD	Standard deviation
SLIT	Sublingual immunotherapy
SMD	Standardised mean difference
SOD	Superoxide dismutase
SR	Systematic review
STAT	Signal transducer and activator of transcription
Syk	Spleen tyrosine kinase
TARC	Thymus-activation regulated chemokine
T-bet	T-box transcription factor
Th1/Th2	T-helper cells1/T-helper cells 2
TLR	Toll-like receptor
TNF-α	Tumour necrosis factor-α
Topo	Topoisomerase
TSLP	Thymic stromal lymphopoietin
VAS	Visual analogue scale
VOMbp	Volatile oil of *flos magnolia biondii pamp*
WAO	World Allergy Organization
WHO	World Health Organization
WM	Western medication
ZGBCQS	Zhong Guo Ben Cao Quan Shu
ZHYD	Zhong Hua Yi Dian

Publications

Yang, A. Y. H., & Kreiner, J. (2015). A clinical monograph of *Radix Bupleuri* (Chai Hu) in B. L. Duke (Ed.), *Chinese Herbs and Herbal Medicine Essential Components, Clinical Applications and Health Benefit* (pp. 190). New York: Nova Biomedical.

Kreiner, J., Pang, E. C. K., Lenon, G. B., & Yang, A. W. H. (2016). *Saposhnikoviae divaricata*: A phytochemical, pharmacological and pharmakinetic review. *Chinese Journal of Natural Medicines*, accepted on 30 May 2016 for publication.

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Summary

Allergic rhinitis (AR) is an allergen-induced immunoglobulin E mediated inflammatory disease that affects approximately 15% of the Australian population. The AR sufferers manifest such nasal symptoms as sneezing, nasal congestion, runny nose and itchy nose. AR has significantly affected patients' quality of life and imposed heavy financial burden to the healthcare system. Current conventional management takes an algorithm approach to introduce different strategies to patients such as education in avoidance of allergen, pharmacotherapy and allergen-specific immunotherapy. However, due to side effects (e.g. somnolence, fatigue, dry mouth syndrome, headache and epistaxis) caused by conventional treatment, more patients are seeking solutions from complementary and alternative medicine including Chinese herbal medicine (CHM).

CHM has been used to manage AR-related signs and symptoms for thousands of years. A number of randomised controlled trials (RCTs) have demonstrated that CHM was effective and safe for managing AR. However, the effects and safety of CHM have not been adequately synthesised and translated to the clinical practice. This project aimed to provide a knowledge base on clinical effects and safety of CHM for the treatment of AR by conducting three reviews on modern and classic literature.

Review 1: Systematic review of RCTs on CHM for the management of AR

This systematic review was performed adhering to the Cochrane Handbook for Systematic Reviews of Interventions. A total of 62 RCTs involving 8,470 participants were included in this review. Results of the outcome measures indicated CHM was highly effective when compared to Western medicine (WM) (37 trials). CHM exerted positive clinical effects in improving global symptoms evaluated across immediate (15 trials), short-term (14 trials) and intermediate (four trials) durations. In the comparison of CHM plus co-intervention with same co-intervention only (17 trials plus three comparisons from three multi-arm RCTs), stronger

clinical effects in improving global symptoms surfaced in CHM combined group in the meta-analyses at immediate (nine trials), short-term (four trials), intermediate (three trials) and long-term (four trials) follow-ups. Assessment of quality of life, use of rescue medication and IgE were limited owing to lack of data in the studies. There were no major side effects reported across all the included studies. The results of the SR surmised that CHM, used orally as alone or adjunct therapy could improve nasal symptoms; particularly CHM combined with co-intervention exerted stronger and prolonged clinical effects in nasal symptom improvement. However, findings are limited by risk of bias within studies and associated with substantial heterogeneity.

The most commonly used CHMs in the clinical studies were also identified through the review process for further investigation of their mechanism of actions. They are Huang Qi (*Astragali Radix*), Fang Feng (*Saposhnikoviae Radix*), Xin Yi (*Magnoliae Flos*), Cang Er Zi (*Xanthii Fructus*) and Xi Xin (*Asari Radix et Rhizoma*).

Review 2: Literature review of experimental studies on mechanism of actions of commonly used CHMs

Five CHMs identified from the Review 1 were further explored for their mechanism of actions by examining the experimental studies. Results of the review revealed these herbs possess characteristics of anti-inflammatory and anti-allergic, analgesic and antinociceptive, anti-oxidative and anti-proliferative, anti-viral, anti-asthmatic, anti-bacterial, anti-gastric, anti-vascular and cardiovascular, anxiolytic and muscle relaxant effects as well as immunoregulatory effects facilitating both immunopotentiating and immunostimulatory activities. The elucidations of the mechanism of actions mapped out its pharmacological actions.

Toxicological evidence of Cang Er Zi and Xi Xin exposed the dangers of renal failures and carcinomas associated with it dosage-related response. Atractyloside and carboxytractyloside were two main toxic constituents in Cang Er Zi, while toxicity of Xi Xin was associated with methyleugenol not aristolochic acid (AA-I) as postulated by many literature on the issue of Chinese herbs nephropathy. Chromatography fingerprinting evidence demonstrated negligible amount of AA-I in Xi Xin. Cases of toxicities were attributed to iatrogenesis, impart due to lack of education by practitioners and lack of surveillance by bodies of authorities. As these two toxic herbs were commonly used for AR management in classical literature, a further exploration of potential CHMs was conducted in ancient texts.

Review 3: Data mining of classical texts on CHM for the treatment of AR-like signs and symptoms

A total of 1,687 articles were included and 294 articles were analysed for of AR-like signs and symptoms associated with use of CHMs in the classical texts of Zhong Hua Yi Dian (ZHYD) and Zhong Guo Ben Cao Quan Shu (ZGBCQS). A sum of 163 herbs was identified for the management of AR-like signs and symptoms in retrospective diagnoses. These 163 herbs were analysed using principal component analysis against 11 AR-like signs and symptoms cited in the classical literature: sneeze, congested nose with runny nose discharge, sinusitis, nasal congestion, itchy nose, allergic rhinitis, postnasal drip, listlessness, headache with eye pain, pain the nose and red nose. Only three components namely, Component 1 (nasal congestion), Component 2 (congested nose with runny nose discharge) and Component 3 (sinusitis) were identified with eigenvalues of more than 1, which were 5.357, 1.235 and 1.029, respectively. The loadings for Components 1, 2 and 3 were 48%, 11% and 9%, respectively. Principal component analyses of the herbs demonstrated Component 1 herbs were Xi Xin, Xin Yi, Bai Zhi, Bai Bu, Cang Er Zi, Chuan Xiong, Fang Feng, Huang Qi, Gua Di, Bo He and Bai Zhu (in descending order) with Component 2 influence in Chuan Xiong, Bai Xian Pi, Gua Di and Huang

Qi (in descending order). Hierarchical cluster analysis also cast Xi Xin as one of the outliers along with Xin Yi with its distinctive pattern. Although it is clustered as an outlier, Xi Xin is correlated with cluster 2 herbs such as Pi Ba, Sheng Jiang, Tong Cao, Bo He, Fang Feng, Gua Di, Bai Zhi, Gan Cao, Cang Er Zi, Chuan Xiong, Huang Qi, Fu Zi, Jie Geng, Nan Xing, Cong Bai, Mu Tong, Gan Jiang, Ren Shen, Qiang Huo and Xiong Huang. All these herbs were grouped together, which could indicate similar characteristics in the management of AR-like signs and symptoms.

Results of this project provide a comprehensive evaluation of clinical effects on CHM for AR management based on evidence from the modern clinical, experimental and classical literature. CHM seems effective and safe for managing AR when used alone or as an adjunct therapy. However, the results need to be interpreted with caution due to limited number of included studies in each comparison with associated high risk of bias and substantial heterogeneity. Seven common herbs (including Huang Qi, Fang Feng, Xin Yi, Bai Zhi, Cang Er Zi, Gan Cao and Xin Xi) identified from modern clinical studies and classical literature may be considered for AR management in future clinical practice and research.

Chapter 1 General introduction

This chapter provides the background, the aims and objectives and rationale of the thesis project. The organisation of the information is also presented in this chapter.

1.1. Background and rationale of the project

Allergic rhinitis (AR) is a bothersome nasal allergy yet it cannot be underestimated as prolonged effects of this disease have many health implications. Currently, the worldwide affliction for this disease accounts for 30% of the adult population, but is rising. Climatic changes, lifestyles and genetic polymorphisms all have a part to play in the rising prevalence of AR. This prevalence has contributed to the atopic march in children as witnessed in the increasing allergies. Epidemiological evidence also demonstrates early onset of AR in childhood is often a cause of concern as development of more severe allergies are likely to set in adolescent years. As a result of prolonged effects of nasal allergy, AR with co-morbid asthma could potentially develop as a long-term condition and impact on overall quality of life. Current clinical diagnosis and conventional medicine for AR treatment are well developed and established but not without its side effects ranging from mild to severe spectrum such as headaches, dry mouth, somnolence and on the severe spectrum, the risk of anaphylaxis. High costs are borne by the individuals and national healthcare systems.

There is a current shift of options in the choice of medicine; end-users of healthcare are turning to alternative medicine. One option is Chinese herbal medicine (CHM), a modality of Chinese medicine (CM), which long been used as an intervention to treat AR in China, Asia Pacific and is increasing in demand in the Western hemisphere. There is evidence of AR-like descriptions in the classical texts of CM, matching the signs and symptoms of modern medicine, therefore indicating that AR is not a new disease but a condition that was well-documented historically.

Historical medical records are important for cross reference of information for clinicians and researchers. It not merely allows examination of retrospective diagnosis and treatment, but also illuminates novel thinking and discovery as to how traditional herbs saturated with bioactive natural compound could treat challenging ailments of today.

This research project is an all-encompassing review of the CHMs in the treatment of AR with CHM. There is a current knowledge gap stemming from a synthesised perspective of modern studies, such as randomised controlled trials (RCTs) and classical use of these herbs. The endeavour of this project is to deliver clinical evidence of the effects of CHMs, analyse the types of herbs used in controlled studies, classically and its pharmacological effects in experimental studies. The followings are the proponents in this project:

1. Clinical studies – identify herbs used in RCTs
2. Experimental studies – identify and elucidate the mechanisms of actions of the herbs commonly used on AR and in other diseases
3. Classical literature – identify herbs used in retrospective diagnosis in ancient times

Overall, the rationale of this review is to produce comprehensive clinical evidence of CHMs owing to the lack of evidence in current literature. It is envisioned that this review would translate evidence from clinical studies to bedside practice for CM clinicians. The synthesised clinical interventions for AR would aid clinical decision in formulation and establish confidence in the use of CHM for AR treatment. A clear and transparent synthesis of this SR would also provide easier accesses to users of CHM for clarification of herbal interventions. Last, in the process of this SR, the efficacious results based on the SR would assist policymakers with evidence-based decision making in the regulation of herbs in the Therapeutic Goods Act in Australia and globally.

1.2. Aims and objectives

The aims of this study are to (1) review the fundamental knowledge of AR from the perspectives of the Western medicine and CM perspectives, (2) investigate the effectiveness and the safety of CHM used for the management of AR by conducting a systematic review (SR) of the RCTs, (3) elucidate the pharmacological effects and the mechanisms of actions of the five herbs commonly used in the RCTs, and (4) extract the herbs used in retrospective diagnosis of AR-like signs and symptoms from the classical texts, conduct pattern analyses of the herbs used classically by employing principal component analysis (PCA) and hierarchical cluster analysis (HCA).

1.3. Organisation of the thesis

This thesis is a composition of three reviews, namely; a SR of RCTs on CHM used for the management of AR, a review on experimental studies and a review of classical literature. The literature reviews of Western medicine and CM are broadly discussed in Chapter 2 and 3, respectively. This chapter provides an overview of fundamental knowledge that pertains to AR.

Chapter 4 discusses the methodologies of the three compositions in terms of search strategies, selection criteria as well as method of extractions and analysis of data.

Outcomes on the three composites are reported in Chapter 5, 6 and 7. Results of SR for the comparators are highlighted in Chapter 5 along with the identification of the principal herbs used in the RCTs. Adverse events of the herbs in the RCTs are also a feature in this chapter. Chapter 6 provides an in-depth review of the effects of herbs examined in experimental studies and its potentiated use in other diseases. The outcomes of the data mining of classical texts and the statistical pattern analyses are discussed in Chapter 7.

Chapter 8 summarises the key findings of three reviews and assesses the overall completeness, applicability and quality of evidence. Detailed comparison with other studies is carried out. The final Chapter 9 highlights the achievements, limitations of this project, examines the significance as well as the implications for clinical practice and future research for AR.

Chapter 2 Literature review on allergic rhinitis (AR) – A Western medicine perspective

This chapter discusses the definition, epidemiology, pathophysiology, impact, comorbidities, classifications, diagnosis and treatment of AR from the perspective of Western medicine.

2.1. Definition of AR

AR is an allergen-induced immunoglobulin E (IgE) mediated inflammatory disease that affects the nasal mucosa membranes (R. Pawankar, Canonica, Holgate, Lockey, & Blaiss, 2013). It is clinically characterised by sneezing, nasal congestion, sneezing, rhinorrhoea and itching of the nose and eyes and/or post nasal drips (J. Bousquet, van Cauwenberge, & Khaltaev, 2001). Exposure to allergens (antigens) which are proteins or chemicals bound proteins elicit immediate IgE hypersensitivity reactions (Abbas, Lichtman, & Pillai, 2012). Typical allergens include grass or weed pollens, pets dander, trees, pollutants and occupational agents (Greiner, Hellings, Rotiroti, & Scadding, 2012). Deifl and Bohle (2011) emphasises that adjuvanticity of these allergens are defined by its enzymatic activity, binding of lipids, interaction with toll-like-receptors (TLR), interaction with non TLR pathogen recognition receptors, dimerization and oligorisation of effector cells. All of these antigenic characteristics are promoters of IgE production in AR.

2.2. Epidemiology of AR

2.2.1. Global prevalence of AR

AR is often regarded as a trivial disease owing to its non-existent fatal rates, however, its prevalence and chronicity is a cause of major illnesses and disabilities worldwide (Ozdoganoglu & Songu, 2012). The Global Alliance against Chronic Respiratory Diseases (2007) reported

400 million persons suffered AR from 1996 to 2006, while the Allergic rhinitis and its impact on asthma (ARIA) guidelines 2010 revision reported AR prevalence was at 10% to 20% of the population, which represented 500 million AR sufferers globally (Brozek et al., 2010). The latest statistics reported in World Allergy Organization (WAO) White Book on Allergy for 2013, global health prevalence for AR adult sufferers ranged from 10% to 30% and children with AR as high as 40% (R. Pawankar et al., 2013). Comprehensive data from Allergies in America, Pediatrics Allergies in America, Allergies in Latin America and Allergies in Asia Pacific compiled detailed prevalence of physician-diagnosed AR based on telephone survey and presented a clear depiction of the percentage of AR sufferers globally (Meltzer et al., 2012) (Table 1). In addition to the prevalence data for children with AR, the multinational studies in Table 1 were surveyed and assessed according to International Study of Asthma and Allergies in Children study methodology by independent projects.

Table 1. Global prevalence of AR

Regions	% of prevalence in adults	% of prevalence in children (years)	Types of reported AR	References
United States of America	14	13 (4-17)	Physician-diagnosed AR	Meltzer et al. (2012)
Latin America	7	9 (4-17)	Physician-diagnosed AR	Meltzer et al. (2012)
Asia Pacific	9	No data	Physician-diagnosed AR	Meltzer et al. (2012)
Thailand **Japan** **Taiwan** **Singapore** **Vietnam**		50.6 (13-14) 32 (13-14) 44.4 (13-14) 25.3 (13-14) 34.9 (13-14)	Self-reported AR	R. Pawankar et al. (2009)
China	20 (11 major cities in China)	9.8 (13-14) (8 cities in China)	Self-reported AR	L. Zhang et al. (2009) (F. Li et al., 2011)
Europe	18.7 (5 European countries only)	No data	Self-reported AR	Canonica, Bousquet, Mullol, Scadding, and Virchow (2007)
Western		20.3 (13-14)		
Northern and Eastern		10.6 (13-14)		
Gulf Arab - United Arab Emirates	32	41(13-19)	Self-reported AR	Alsowaidi, Abdulle, Shehab, Zuberbier, and Bernsen (2010)
Eastern Mediterranean	No data available	19.5 (13-14)	Self-reported AR	Ait-Khaled et al. (2009)
Oceania	No data available	24.4 (13-14)	Self-reported AR	Ait-Khaled et al. (2009)
Australia	15	47.7 (13-14) (1 city only)	Self-reported AR	Australian Institute of Health and Welfare (2011) Ait-Khaled et al. (2009)
New Zealand	No data available	18.8 (13-14)		Ait-Khaled et al. (2009)
Indian sub-continent	No data available	18.5 (13-14)	Self-reported AR	Ait-Khaled et al. (2009)
Africa **Algeria** **Cameroon** **Congo** **Cote d'lvoire** **Ethiopia** **Gabon** **Kenya** **Nigeria** **Republique du Congo** **Reunion Island** **République de Guinée** **South Africa** **Sudan** **Togo** **Tunisia**	No data available	28.9 (13-14)	Self-reported AR	Ait-Khaled et al. (2009)

2.2.2. Prevalence of AR in Australia

In Australia, AR is one of the most prevalent respiratory conditions affecting 15% of the population; one in seven people at an estimated 3.1 million people suffer AR as a long-term health condition from 2007 to 2008 (Australia Health Bureau Statistics, 2012; Australian Institute of Health and Welfare, 2011). In terms of gender differences, AR prevalence in females was 1.1 times higher than males; with the former 1.7 million and the latter 1.5 million, both sexes suffering AR as a long-term condition in Australia from 2007 to 2008 (Australia Health Bureau Statistics, 2012). Although it should be noted that this statistics may not be of significance as there may be under-reporting in AR-related cases with males population in remote regions and also associated-psyche of reluctance of seeking help or reporting ailments for fear of being labelled as being weak (Ricciardelli, Mellor, & McCabe, 2012). In addition, percentage of AR prevalence for children in Australia was not available for the country as a whole, only Melbourne city was assessed, with an astonishing high prevalence of 47.7% (Table 1). To date, no current data on AR prevalence have been updated in Australia nor prevalence for children with AR are available.

2.3. Risk factors of AR

IgE allergenic reactivity in AR were linked to environmental-induced risk factors such as pollens, cypress, birch, animal dander, dust mites, cockroaches and moulds as well as occupational risks that include chemicals and toxic and non-toxic materials (Greiner et al., 2012). Meltzer et al. (2012) noted the top three common triggers affecting AR sufferers were pollen, dust and grass pollens. In the United States, a survey conducted by the Allergies of America discovered respondents ranked the top ten triggers that cause AR which included, pollen (41%), dust (34%), grass (22%), weather (22%), animal dander (18%), damp/mould/mildew (11%), perfume (6%), tobacco smoke (6%), plants/trees/leaves (6%) and fumes (5%) (Figure 1).

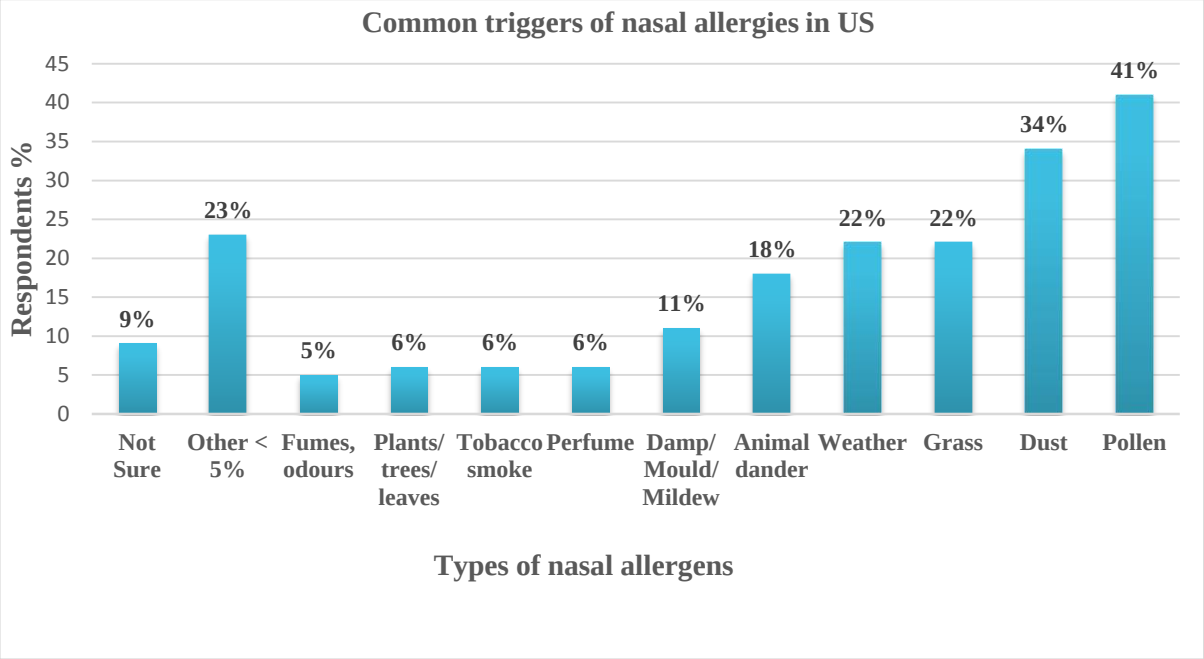


Figure 1. Common triggers of nasal allergies in US (data adapted from Fig. 1. on page S117 of Meltzer et al., 2012)

In Latin America, dust was cited as the highest trigger by 55% of the respondents, while contrary to Asia Pacific, climate and humidity were main triggers by 55% of respondents, respectively (Figure 2). This could be generated by the outdoor pollutants in the changing modern landscape associated with city-living which Asia Pacific is undergoing rapid economic development and westernisation (Wong, Leung, & Ko, 2013).

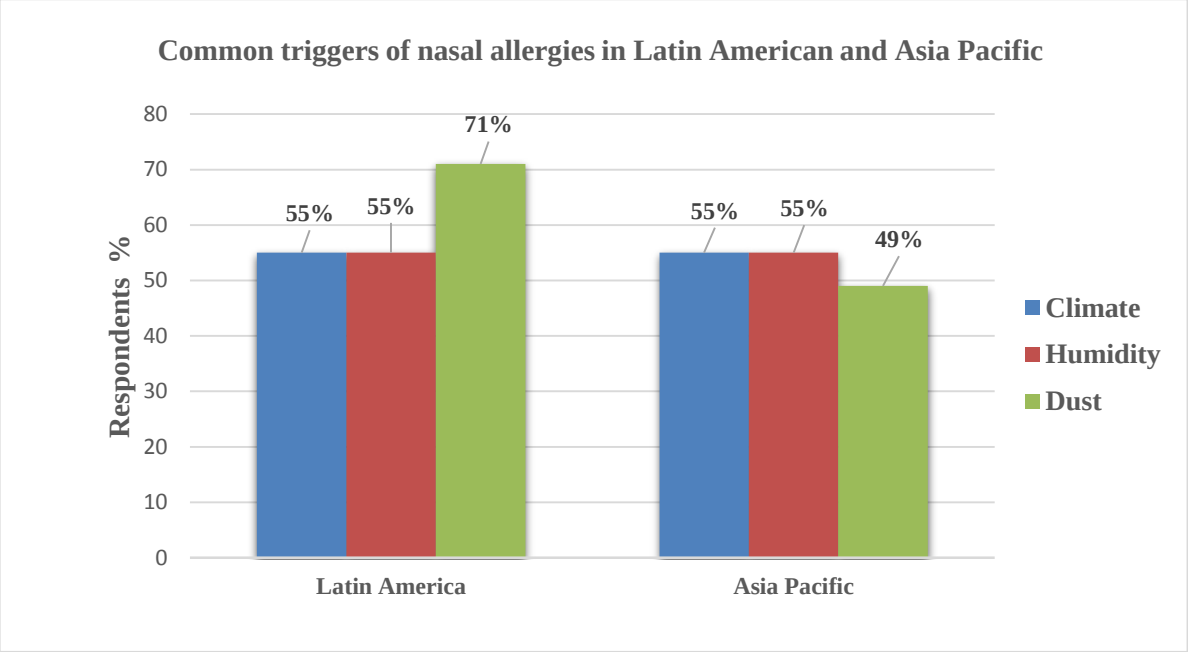


Figure 2. Common triggers of nasal allergies in Latin America and Asia Pacific (data extracted from page S118 of Meltzer et al., 2012)

2.3.1. Indoor pollutants

Exposure to both indoor and outdoor pollutants is associated with new onset of rhinitis, rhinoconjunctivitis, asthma and asthma exacerbation and acute respiratory infections. One source of indoor pollutants lies in the housing characteristics of the accommodation. Housing characteristics of the accommodation refer to the fabric of the house, namely; its ventilation, renovation, decoration works and its maintenance, and presence of plants, all of which may influence the indoor air quality.

Poorly ventilated housing with indoor damp and dust mites can result in an insidious onset of AR and other allergic conditions. The high humidity in the ambient air fosters proliferation of mould and dust mites. Poorly insulated housing, lack of indoor aeration and reduced indoor heating during cold winters contribute to high humidity. The most common indoor moulds are *Cladosporium*, *Aspergillus* and *Alternaria*, *Pencillium* (Curtis, Lieberman, Stark, Rea, & Vetter, 2004; Dallongeville et al., 2015).

These fungi or moulds are dispersed by airborne spores that thrive on moistures. Studies have shown that AR and comorbidities such as rhinosinusitis, wheezing and allergen-related asthma are associated with exposure to these airborne or dustbourne moulds concentrations (Baldacci et al., 2015; Norback, Lampa, & Engvall, 2014). One French study investigated the allergenic risk factors of moulds concentration in dwellings (Dallongeville et al., 2015). Age of building, ventilation, heating, ambient humidity, temperature and carbon dioxide concentration as well as pets, plants signs of dampness and smoking were considered as evaluation parameters. Results revealed that the level of fungal concentration coincided with the presence of plants in living rooms in cold seasons. *Cladosporium* and *Penicillium* were the most prevalent genera of the fungi found in homes (Dallongeville et al., 2015). Cold winters influenced the growth of *Aspergillus* and *Penicillium* in living rooms while *Aspergillus* and *Alternaria* were higher in bedrooms. Dampness and indoor smoking were associated with higher *Penicillium* concentrations. Interestingly, R. Pawankar et al. (2013) indicated that the presence of carpeting and flooring type had no impact whatsoever on dust mould concentration. Evidence concluded that presence of pets were significantly associated with allergens concentration (Baldacci et al., 2015). Therefore, allergens within indoors can be insidiously introduced owing to the interior and the structure of the dwellings and contribute to AR and comorbidities.

2.3.2. Outdoor pollutants

Apart from the well-established evidence based environmental-induced causal link to grass pollens, mould, cypress, birch, animal dander, dust mites, and cockroaches, the environmental risk factors for IgE sensitization has increased. The challenge of global warming has lately been cited as the cause of outdoor air pollution leading to rise in ambient particulate matters as well as carbon dioxide and ozone pollution (R. Pawankar et al., 2013). Global warming, a contributory factor of outdoor pollution is an important risk factor of AR. Climatologic changes have prompted a change in the seasonal count of pollen production, dispersion and the transport

of these aeroallergens. Sensitization to pollen aeroallergens is undisputedly one of the risk factor of IgE-induced AR. A randomised controlled parallel group study of children (aged 6 to 11 years) with seasonal AR (SAR) from 15 countries including US, Europe and Southern hemisphere revealed that pollens were the most common group of allergen ranging from 28% to 100% in all countries, other than Israel (Baena-Cagnani et al., 2003). The increased pollen counts geographically in these countries is highly attributed to extreme changes in weather patterns such as increasing heat waves, unpredictable floodings, thunderstorms and rainfalls (D'Amato et al., 2015). Based on the Working Group I report of the Intergovernmental Panel on Climate Change, the spike in temperature from 2003 to 2012 led to an increase of heat waves rising to 35ºC and greenhouse gas concentrations (D'Amato et al., 2014). Global meteorological analysis by the US National Oceanic and Atmospheric Administration reported the warmest January to October period in 2015 since 1880, creating climatic anomalies driven by El Niño and rising sea temperature globally (Australian Government Bureau of Meterology, 2016). The repercussions of global warming have an impact on the generation and dispersion of pollen and air pollution, all of which correlated to increasing AR, atopy and asthma. Extreme changes in weather have favoured an elevation of length and the severity of the pollen season. The increase of thunderstorms can induce severe asthma attacks in AR patients. These episodic days known as thunderstorm outflows, trigger a dispersion of allergenic particles from pollens and spores caused by the osmotic rupture, which are induced by the heightened intensity and the frequency of the heavy rainfall (D'Amato et al., 2014). It is posited that during these epidemic days, a marked increase in the patients affected by the pollen concentration was observed in cases of AR, allergic asthma exacerbation and chronic obstructive pulmonary disease. Incidences of the respiratory attacks in AR and asthma cases were recorded with the onset of thunderstorm outflows in London 1994, Wagga Wagga 1997 and Naples 2004 (D'Amato et al., 2015). A recent severe thunderstorm outflow occurred on 20 November 2016 in metropolitan Melbourne and outer regions in Victoria led to an unprecedented eight fatalities and one in critical care for

nine days (Livingston & Drape, 2016). Thousands of people suffered from ‘thunderstorm asthma’ because of the increased pollen dispersions in the ambient air. This was the worst thunderstorm recorded in history which resulted in 8,500 patients admitted to hospital and 30 patients in critical care unit in one night (Livingston & Drape, 2016).

Aside from thunderstorm outflows, heat waves are also causing more desertification and sandstorms as witnessed on yearly basis in Beijing and other parts of China. Sand particulates can cause respiratory dysfunction and AR. The Asian sand storm (ASD) is common during spring in North Western and Eastern regions of China. The occurrences of the ASD affect the Korean Peninsula and Japan annually. The chemical compounds comprise of sulphate, nitrate and microbes in the alkaline soil of ASD (T. Ichinose et al., 2009). These airborne sand particulates in ASD pose as an aggravating risk factor for AR sufferers. Combined exposure to ASD and Japanese cedar pollens induces and aggravates AR exhibited an exponential increase by 35.5 fold compared to control. Enhanced histamine levels of four-fold were also detected in nasal cavity lavage fluids (T. Ichinose et al., 2009). Pathological evidence unveils the impact of ASD on nasal mucosa with extensive proliferation of eosinophil and goblet cell infiltration in the nasal subepithelium, with the latter inducing mucous production and the former augmenting chemotactic and chemokine proteins release interleukin (IL)-5, monocyte chemotactic protein-3 and eotaxin in the bronchoalveolar lavage fluids (T. Ichinose et al., 2008). The evidence suggests meteorological changes in terms of temperature, wind speed, and thunderstorms can influence pollen counts and exert a priming effect on AR.

Ambient particulate matters (PMs) in air pollution are a contributory risk factor in the current modern lifestyle. PMs refer to make up of chemicals and organic particles such as carbon dioxide, nitrogen dioxide, sulphur dioxide and other toxic compounds found in the emissions of motor vehicles or biofuel mass production (Laumbach & Kipen, 2012). Diesel exhaust

particles produced from emissions of motor vehicles made up a large proportion of PMs. Studies have found that PMs with aerodynamics diameter of ≤ 2.5 μm pose a potent threat to respiratory diseases (Laumbach & Kipen, 2012; Leung, Ko, & Wong, 2012). With regular and uncontrolled exposure to these toxic air particulate, priming of eosinophilia can lead to atopy.

2.3.3. The hygiene hypotheses: A changing perspectives

The hygiene hypothesis proposes that decreased exposure to cross-infections in early life increases the risk of developing AR and other allergic diseases. The increase of atopic diseases and AR is largely attributed to reduced exposure to environmental micro-organisms such as multi-cellular parasites owing to changed lifestyle in developing countries (Kramer et al., 2013). An epidemiological study conducted by European Community Respiratory Health Study (ECRHS) which involved 22 countries, indicated increasing AR attributed to hygiene hypothesis could elevate the incidence of developing AR in adulthood (Matheson et al., 2011). Early life factors include gender, geographical dwellings, environmental pollution, no siblings, late entry to preschool or nursery, maternal smoking and lack of exposure to pets present could be a determinant for AR incidence in later stages of life (Matheson et al., 2011). Gender is a strong risk factor- it appears females tend to develop rhinitis in later childhood with more incidence of rhinitis in adulthood. Crude lifelong incidence of rhinitis was 7.00/1000/year for men and 7.95/1000/year for women (Matheson et al., 2011). Females tend to suffer from chronic long-term AR, insofar, there is a gap of knowledge as to why females tend to be more susceptible than males in later stage of childhood. Geographical dwellings, pets ownership and exposures to animals such as farm living also conferred a protective effect against development of atopic allergies and AR in adulthood. City living encumbered with exposure to ambient pollution produced by biofuel and diesel emission could potentially increase priming of the immune system (Laumbach & Kipen, 2012).

Recent studies have proposed corollary perspectives to the hygiene hypothesis in view of the changing landscape of modernisation and lifestyles. Two foremost hypotheses put forth to the extension of hygiene hypothesis were the "old friends" hypothesis and the "microbial deprivation hypothesis" (Bloomfield et al., 2016). Both involved microbiota and microbiomes and are inextricably intertwined. Microbial deprivation hypothesis stipulated that deprivation of the non-pathogenic beneficial microbes were associated to many autoimmune and allergic diseases, not the least AR as a chronic condition. Microbiota is regarded as the totality of all microorganisms in a metaorganism system while microbiomes refer to the combined genetic material of the microbiota (Jenmalm & Björkstén, 2016). Microbiota forms a symbiotic interdependency in the immune system. Early exposure to the microbiota enables the adaptive immune system the capacity to recognise non-pathogenic and pathogenic microbes, creating a complex interdependency for an immune environment to ward off atopies in later life. Immunologically, the proposed notion suggests that an early immune challenge to bacteria and viruses could essentially be priming the immune system towards a stronger T helper cell 2 (Th2) pro-allergic responses and an attenuated Th1 proinflammatory responses in later life. Microbiomes is defined as the sum of genetic information in microbiota (Jenmalm & Björkstén, 2016). Evolutionary changes and adaptive nature of the microbiome included non-pathogenic commensal microbiota such as *Firmicutes*, *Tenericutes*, *Proteobacteria*, *Bacteroidetes*, *Actionbacteria* and *Fusobacteria phyla* (Jenmalm & Björkstén, 2016). The evolution of these commensal pathogens exerts complex human microbial ecosystems in the individual's immune system by conferring an adaptive effect over pathogenic invasion. Reduction of the colonisation of these microbiota and microbiome development owing to urban living and low dietary fibre has led to a long-term impact of autoimmune and allergic diseases. Therefore, the increasing prevalence of AR as a chronic condition could in part be due to these hypotheses in our times.

2.3.4. Genetics and environment

Genetics and environmental interactions have been postulated to be inextricably linked to the development of AR. "Atopic march" was described as increased sensitization to environmental stimuli such as pollens, traffic pollution or other outdoor pollutants that could give rise to other allergies. The proposed notion is that prolonged allergen sensitisation could alter gene phenotypes and lead to a Th2 dominant immune system, manifested in the development of chronic AR.

Genetic linkage in families with IgE predominance could be susceptible to sensitisation of IgE-specific allergens. Emerging projects have begun to employ genome-wide studies to locate the single nucleotide polymorphisms across the genome to identify susceptible genes which are likely to develop AR or other allergic diseases (Andiappan et al., 2013; Marie-Hélène Dizier et al., 2007; Ramasamy et al., 2011). C11orf30/LRRC32, BCAP, MRPL4 and TME232/SCLA25A56/TSLP are definitive susceptible genes for AR (Andiappan et al., 2011; Ramasamy et al., 2011). The mechanism for C11orf30 and LRRC32 related to the epithelial barrier function, regulatory T-cell functions and immune tolerance, while TME232/SLA25A/TSLP were associated to IgE levels to grass sensitisation (Portelli, Hodge, & Sayers, 2015). Both C11orf30 and LRRC32 potential function are related to the tetraspan proteins which are membrane-associated molecules that span the membrane four times and these teraspanins act as "molecular facilitators" for signalling complexes and transporters (Mahmudi-Azer, Downey, & Moqbel, 2002). BCAP, a cytosolic adaptor that connects B-cell receptor, is implicated in the immunoregulatory function of B cells survival while MRPL4, plays a significant role in adhesion inflammatory process (Portelli et al., 2015) and hypoxia-inducible factor 1-α downstream cascade (Andiappan et al., 2011). Overlap genes in studies suggested a potential linkage of AR with the development of allergic diseases such as asthma

and atopic dermatitis although many studies have noted heterogeneity exists in the investigation process (Table 2).

Table 2. Summary of susceptibility genes and loci of AR

Genes	Loci	Associations	Functions	Shared regions/ associations	References
C11orf30/LRRC32	11q13	AR Grass sensitization	Regulates gene expressions, epithelial barrier/ regulatory T-cell function	AR Asthma Atopic dermatitis	J. Li, Zhang, and Zhang (2015) Portelli et al. (2015) Ramasamy et al. (2011)
TME232/ SCLA25A56/TSLP	5q22	AR Grass sensitization	Tetraspan protein/ transporter/ activates dendritic cells	AR Atopic dermatitis	J. Li et al. (2015) Portelli et al. (2015) Ramasamy et al. (2011)
MRPL4	19p13.2	AR	Inflammatory adhesion process	AR	Andiappan et al. (2011)
BCAP	10q24	AR	Activation and development, and maturation of B cells	AR	Andiappan et al. (2011) J. Li et al. (2015)
FCER1A	1q23	Total IgE	Alpha chain of the high affinity FcεRI	AR Asthma	Portelli et al. (2015) J. Li et al. (2015)
IL13/RAD50	5q31	Total IgE	Cytokines in IgE class switch/ DNA repair	AR Asthma Atopic dermatitis	Portelli et al. (2015)
HLA DRB4	6p21	Grass sensitisation	T-cell responses	AR	Portelli et al. (2015)
HLA DRB1	6q21	Total IgE	T-cell responses	AR	Portelli et al. (2015)
HLA G	6q21	Total IgE	T-cell responses	AR	Portelli et al. (2015)
HLA-A	6q21	Total IgE	T-cell responses	AR	Portelli et al. (2015)
HLA-DQA2	6q21	Total IgE	T-cell responses	AR	Portelli et al. (2015)
STAT6	12q13	Total IgE	Signal transduction linked to IgE synthesis	AR	Portelli et al. (2015)
IL4R/IL21R	16p12	Total IgE	IgE regulation via IL4 and IL21	AR	Portelli et al. (2015)

The atopic triad of AR, asthma and atopic dermatitis could be detected in the overlapped or shared associations within the loci of genes. The discovery of these susceptibility genes for incidence of AR in adulthood supported epidemiological findings that atopic march could be triggered with the hygiene hypothesis. Therefore, owing to presence of susceptibility AR genes and environmental factors at play, genetics-environment interaction could be a determinant factor of early life onset of AR and development of long-term AR or other allergic diseases at later life.

2.4. Pathophysiology of AR

2.4.1. Pathomechanism of AR

Allergen interactivity induces IgE hypersensitivity. IgE hypersensitivity is caused by mast cells and basophils with a high affinity *Fc* receptor specific for ε heavy chains, FcεRI (Abbas et al., 2012). Cross-linking of FcεRI molecules activates degranulation of mast cells and basophils to produce an inflammatory-mediators release, secretion and synthesis of cytokines and chemokines and lipid mediators (Abbas et al., 2012; R. Pawankar, Mori, Ozu, & Kimura, 2011). Chronic AR mainly involves Th2 and Treg, both thymus-derived and share cluster of differentiaton $(CD)_4$ surface membrane markers (Osguthorpe, 2013). Atopy is closely indicated and linked to upregulation of Th2 that triggers cytokines and causes systemic inflammation. Thymic stromal lymphopoietin (TSLP) is essentially the master switch for Th2 differentiation, responsible for maturation of dendritic cells and recruitment of eosinophils. Both chemokine ligands (CCL) 17 and CCL 22 as well as thymus-activation regulated chemokine (TARC) act as chemoattractant facilitated by the binding to C-C chemokine receptor 4 on the cell surface to further promote accumulation of clonal Th2 cells response (Figure 3).

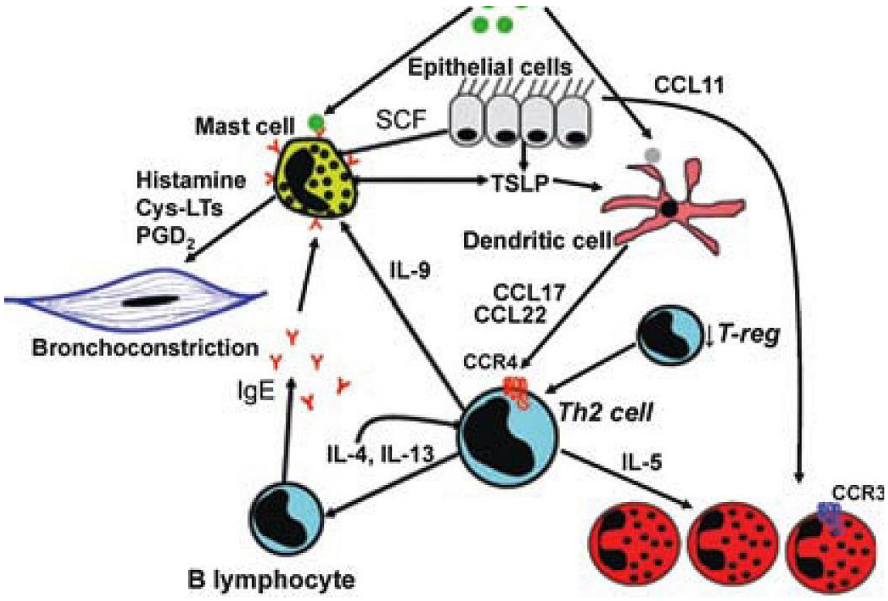


Figure 3. Pathomechanism of AR (extracted from Figure 2 on pg 387 of Osguthorpe, 2013)

Differentiation of Th2 cells can be initiated through several pathways: cell contact with major histocompatibility complex (MHC) type II cell surface and cell epitope on cell surface, CD80, CD86, CD28 on antigen presenting cells and T-cells or interleukin (IL)25, IL33 cytokine-driven Th2 differentiation, IL4 stimulatory-activation and last, APCs direct stimulation of B-cells with IgE productions. These cytokines exhibited an interplay of different functions: IL4 is involved in class switching B-cells to IgE producing plasma cells and it recruits eosinophils and basophils; IL5 also recruits eosinophils and prolongs its lifespan; IL9 proliferates mast cells; IL13 stimulates goblet hyperplasia and secretes chemoattractant to dendritic cells and induces B-cells toward IgE production as well as granulocytes macrophage colony stimulating factor (Osguthorpe, 2013) (Figure 3).

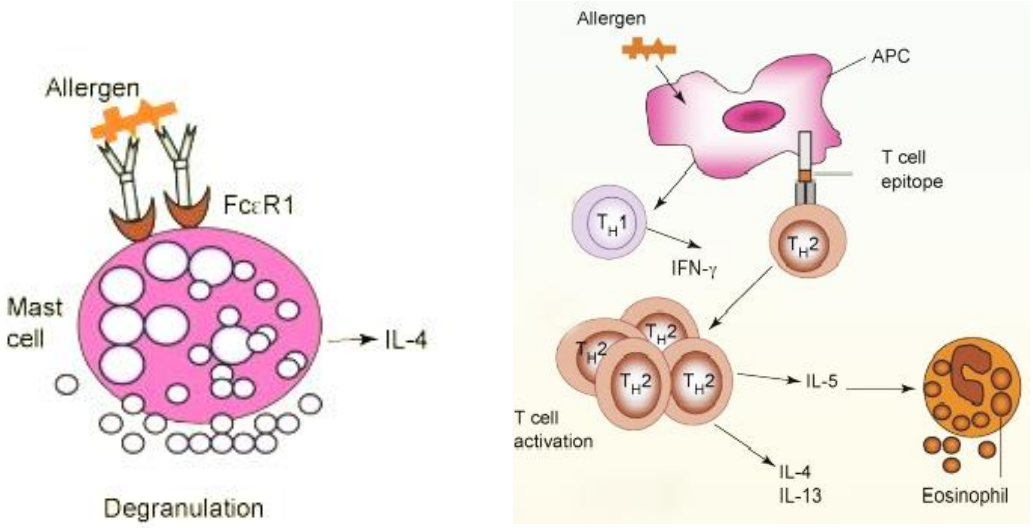
Immunologic studies have long postulated IgE synthesis took place at the site of bone marrow, splenic tissues and blood (Abbas et al., 2012; R. Pawankar, Mori, et al., 2011). In fact, IgE synthesis also occurred at the nasal mucosa with a marked increase of cells expressing local IL4 messenger ribonucleic acid (mRNA), IgE heavy chain (Cϵ) and IgE heavy chain promoter (Iϵ) ribonucleic acid (RNA) after pollen provocation. Iϵ-RNA is the hallmark for B cells target

for class switching to IgE. Genome isotype class switching and VD)J recombination caused deletion of Iϵ, replacing it with Cϵ, expressed at the B-cells (L. A. Cameron et al., 1998). B cells count, IL4 and CϵRNA and Iϵ transcripts in the biopsy of nasal mucosa obtained from 33 subjects with seasonal and non-seasonal response to topical glucocorticosteriod treatment were analysed. The outcome of this study indicated that the marked increase of cells expressed IL4, Cϵ and Iϵ RNA within the nasal mucosa of patients with AR. Increased Cϵ and Iϵ B cells showed production of IgE in the nasal mucosa, however its origination is unknown. Effects of AR were also attenuated with the use of the gluccocorticosteriod treatments, which reflected the decrease of the IL4 and Iϵ RNA, indicating a halt in the transcription of Iϵ to Cϵ germline transcript. It strongly confirms that IgE synthesis may take place locally producing in situ inflammation in patients with seasonal AR (L. Cameron et al., 2000; Gevaert et al., 2013; Smurthwaite & Durham, 2002; Takhar et al., 2005) as well as systemic inflammation in the upper and lower airways (R. Pawankar, Mori, et al., 2011).

2.4.2. IgE inflammatory mechanism – Early phase

IgE interaction involves molecules MHC-II along with antigen-presenting cells such as macrophages and dendritic cells co-presenting IgE specific allergens to $CD4^+$ T cells. Early exposure to allergens promotes cross-linked IgE molecules on cell surfaces and this in turn triggers an immediate reaction resulting in the degranulation of mast cells and mediators (Figure 4). Histamines, leukotrienes, plate-activating factor, prostaglandin D_2 (PDG_2), are some major vasoactive mediators that trigger an immediate inflammatory in AR (R. Pawankar, Mori, et al., 2011). Sensitisation takes place with recurrence of allergen exposure. This phase is known as the early phase reaction (R. Pawankar, Mori, et al., 2011). Concentrations of chemical mediators in nasal secretions after nasal allergen challenge (NAC) and during nasal allergic exposure were indicative of the role of mast cell in early phase inflammation (D. Wang, Clement, Smitz, & Derde, 1995) (Figure 4). Mast cell-driven mediators, histamine, tryptase,

PGD_2 and leukotriene (LT) C_4 and kinins significantly peaked after five minutes of NAC. Predominant symptoms of allergies that occurred during this phase were the onset of sneezing and itching. Time span for early phase reactivity after NAC was observed to almost start immediately after five minutes of allergen exposure and could last more than an hour (D. Wang et al., 1995).



Early phase reaction **Late phase reaction**

Figure 4. Early and late phases reaction of AR (extracted from Figure 1 on page 154 of Bhalla & Singh, 2008)

2.4.3. Systemic inflammatory mechanism of AR – Late phase

Late phase reactivity is a latent eosinophils-inflammatory response that results in the chronic AR, characterised by nasal congestion with little sneezing and rhinorrhoea (R. Pawankar, Mori, et al., 2011; D. Wang et al., 1995; D. Y. Wang & Clement, 2000). Late phase reaction in AR is characterised by severe nasal blockage within four to 10 hours of exposure. Nasal congestion is one of the clinical symptoms that characterises late phase reaction in AR patients. D. Wang and Clement (1995) discovered 17 out of total 18 atopic subjects experienced immediate unilateral or bilateral nasal obstruction along with sneezing and rhinorrhoea. Four types of nasal reactivity were detected within 10-hour fluctuation resistance such as no late phase, no major increase in one or both nasal cavities, one-sided nasal blockage and alternating nasal cavities.

Results indicated during the late phase bilateral obstruction occurred in median of 41%, unilateral obstruction in median of 82% while the most common alternating type is the median of 47%. Unilateral nasal obstruction during early phase is at 94%, and late phase is at 84%. Severe nasal blockage was experienced within four to 10 hours of exposure for late phase atopic patients.

Nasal congestion is one of the clinical symptoms that characterises late phase reaction in AR patients while during the early phase, nasal congestion is normally accompanied with sneezing and rhinorrhoea (D. Y. Wang & Clement, 2000). The key driver of late inflammatory response lied in the production of eosinophil cationic protein (ECP). Increase of the eosinophils and ECP concentrations mediated by the IL5, IL4 and IL13 in Th2 differentiation were detectable in the nasal secretions (Figure 4). Both concentrations of eosinophils and ECP peaked at two hours and lasted for eight hours. Highest concentrations of ECP were reached after 24 hours with no clear signs of plateau. This indication strongly emphasised the role of eosinophils in late phase reactivity in pathophysiology of chronic AR. Clinically, nasal congestion could be used as a qualitative (types of nasal obstruction) and quantitative (biopsies of nasal mediators) diagnostic tool for AR.

2.4.4. Theory of a 'unified airspace' inflammatory respiratory model

The theory of the "unified airspace" has been endorsed by World Health Organization (WHO) collaborative health workgroups such as ARIA and WAO. Inflammation of the upper and lower airways shares similar pathologies as well as affliction of inflammation in the respiratory system. The pathophysiology of AR is characterised by the inflammation of the nasal mucosa with the involvement of the upper airways, while asthma involves inflammation of the pulmonary airways and bronchial hyperresponsiveness. A 23-year follow-up epidemiological research demonstrated the link between the development of AR and asthma was intertwined in

a cohort of 378 university students. Results demonstrated the activity of asthma occurred concurrently with the occurrence of AR. Improvement of AR symptoms with resolution of asthma and exacerbation of AR was concurrent with worsening of asthma symptoms (Greisner, Settipane, & Settipane, 2000).

The unified airspace is essentially defined by the concept of the one airway disease. Both the nose and the bronchi share similar inflammatory mechanism. Specific adhesion molecule ICAM-1 (CD54) expressed on the epithelial and endothelial cells was essentially involved in the inflammation of the mucosa cells in the early phase reaction. This inflammatory infiltrate continued to exist causing minimal persistent inflammation even though allergen provocation had subsided (Compalati & Ridolo, 2010). Even so, an experimental study demonstrated moderate to severe persistent AR contributed to the worsening of asthma by enhancing lower airways inflammation irrespective of the intra-nasal corticosteroids prescribed to subjects (Oka et al., 2014). High levels of exhaled nitric oxide fraction were sustained indicating activity of atopic AR. Visual analogue scale (VAS) for nasal symptoms corresponded with the elevation of exhaled nitric oxide fraction levels. This study underscores the link of AR and asthma as well as atopic AR as a contributor to the exacerbation of asthma.

2.5. Impacts of AR

2.5.1. Quality of life

AR comorbidities can severely impair overall physical, emotional and social aspects of life, causing lower vitality and poorer general health (de la Hoz Caballer et al., 2012; Leynaert, Neukirch, Liard, Bousquet, & Neukirch, 2000). The costs of AR extend beyond the individual suffrage. In fact, the costs incurred are far-reaching and burdensome to both individual and society. Poor physical symptoms associated with AR can encumber cognitive processes in terms of memory, psychomotor skills and performance (Blaiss, 2000). Mood disturbance,

daytime somnolence, fatigue and irritability owing to sleep disturbance are often associated with nasal congestion. A survey conducted by Meltzer et al. (2012) found that nearly one in four US adult respondents (22%) reported to experience sleep disturbance; similarly one half of the Latin America adults (44%) and more than 70% of the Asia Pacific reported to be suffering from sleep problems. Learning deficits in chronic AR are manifested in poor decision making, slow psychomotor and verbal learning. AR has a profound impact on the emotional health of sufferers. Emotionally, the respondents involved in the surveys reported 8735 US adults with AR felt miserable (65%), irritable (64%), depressed (36%) or embarrassed (23%) during the allergy season. Both adult respondents in Latin America and Asia Pacific were reported to suffer from depression, 17% and 16% respectively (Meltzer et al., 2012). This emotional impact limits the social lifestyle of AR sufferers. More than one third of the US adult AR sufferers (35%) interviewed noted they avoided activities because of their nasal allergies. Similarly, Latin America adult respondents (16%) reported limitation and restriction in their ability to participate in social activities and Asia Pacific respondents cited indoor (9%) and outdoor (7%) activities. Significant impact of AR on overall quality of life affects physical, mental and emotional health (Australian Institute of Health and Welfare, 2011; de la Hoz Caballer et al., 2012).

2.5.2. Burdens of AR

Besides impacts on quality of life, AR has significant bearing on direct and indirect costs of healthcare. Direct costs are expenses associated with the course of managing the disease that include physician fees, any laboratory procedures, allergen testing procedures, pharmaceutical agents and allergen immunotherapy (Blaiss, 2010). Hidden costs refer to monies spent related to managing the comorbidities of AR and the exacerbation of the disease including treatment in X-ray screenings and emergency department visits for rhinosinusitis, surgical costs for nasal

polyps, and medical costs for otitis media (Gupta, Sheikh, Strachan, & Anderson, 2004; Nathan, 2007).

In United Kingdom (UK), one study indicated mean weekly visits to GP episode incidence rates for AR treatments in 2002 was 25 per 100,000 for AR sufferers and nasal allergy made up 4.3 million out of 66.5 million community prescriptions dispensed (Gupta et al., 2004). Direct cost for UK National Health service for managing allergy was estimated over one billion UK pounds (equivalent to AUD $2 billion) in 2002 (Gupta et al., 2004). In the United States (US), the cost of treating AR is substantial. Overall AR-related direct costs had nearly doubled from US $6.1 billion (equivalent to AUD $7.9 billion) in 2000 to US $11.2 billion (equivalent to AUD $14.6 billion) in 2005 (Meltzer & Bukstein, 2011). More than half of the costs were accrued to prescription medications. Total direct medical cost was estimated at $3.4 billion (equivalent to AUD $4.4 billion), with a large proportion attributed to prescription medications (46%) and outpatient visits (51.9%) (Meltzer & Bukstein, 2011). Latest figures of 2007 and 2011 indicated costs of burden for AR in the US had increased by 2.3 billion within 5 year-span period in total estimated costs and this amount was expected to rise (Table 3).

Table 3. AR burden of costs in AUD (Data from Ruby Pawankar, Canonica, Holgate, and Lockey (2012)

Countries	Year of costs calculated	Population	Diseases	Direct costs	Indirect costs	Total costs estimated
Australia	2007	23 m	All allergies	$1.1 b	$ 8.3 b	$ 9.4 b
	2001		AR	$107.8 m		
	2010		AR	$226.8 m		
Finland	2005	5.3 m	All allergies	$686 m	$75.8 m	$761.7 m
South Korea	2005	50 m	Asthma	-	-	$2.3 b
			AR			$344 m
Israel		7.5 m	Asthma	-	-	$45 m
Mexico	2007	103 m	Asthma			$45 m
USA	2007	310.2 m	Asthma	$19 b	$6.4 b	$25.5 b
	2011		AR	$14.6 b	Up to $9.7 b	Up to $27.8 b

Notes: b: billion; m: million

In Australia, AR-related costs data are not readily available, however wholesale costs of AR medications depicted the demand costs over the years. Wholesale cost to community pharmacies of intranasal corticosteroids and oral histamines doubled from AUD $107.8 million in 2001 to AUD $226.8 million in 2010, over a span of ten years (Table 3). Wholesale cost of over-the-counter (OTC) medications per person for oral histamines has increased from AUD $4.40 to AUD $7.48 and intranasal corticosteroids increased from AUD $1.15 to AUD $2.68 (2.3 times), from 2001 to 2010 (Australian Institute of Health and Welfare, 2011).

2.6. Comorbidities of AR

AR symptoms range from mild to severe spectrum and adverse comorbidities associated with AR can severely impact on the quality of life. Asthma, stress (Lee, Chung, Shin, Kim, & Cho, 2008), sleep apnoea (Benninger & Benninger, 2009), sleep disturbance (J Bousquet et al.,

2008), fatigue, otitis media with effusion, nasal polyposis, rhinosinusitis and chronic rhinoconjunctivitis (R. Pawankar, Canonica, Holgate, & Lockey, 2011) are some of the health comorbidities of AR.

2.6.1. From AR to asthma

According to the WAO, AR is considered a risk factor for asthma (R. Pawankar, Canonica, et al., 2011). Studies have shown a distinct possible link of early onset of AR in childhood to the development of asthma with concomitant AR in later years (Ciprandi, Signori, Tosca, & Cirillo, 2011; Compalati & Ridolo, 2010; Matheson et al., 2011; Westman et al., 2014). Ciprandi et al. (2011) termed this as an indicator of an "asthma march". AR and asthma are inextricably linked, owing to long childhood risk factors and genetic disposition of individuals. The incidence of asthma is dependent on the onset of AR by seven years of age, and asthma incidence was more than three times in those with childhood AR compared to those who never suffered from childhood AR (Burgess et al., 2007). Many studies have also indicated there is a co-existence of AR and asthma (Burgess et al., 2007; Greiner et al., 2012; Greisner et al., 2000; Linneberg et al., 2002). In Australia, about 80% asthma sufferers experience AR (Asthma Australia, 2014). A Swiss-linked AR study in asthma confirmed 76% asthmatic patients suffered from AR (Taegtmeyer et al., 2009). Approximately 19-38% of patients with AR have concomitant asthma and 30-80% of asthmatics (Compalati & Ridolo, 2010). There is a strong body of evidence suggesting a strong linkage between AR and asthma.

2.6.2. Sleep disturbance and fatigue

Sleep disturbance has been cited by AR sufferers as one of the main comorbidities that affects their quality of life. In Asia Pacific, sleep disturbance was the main symptom that affected sufferers, whilst in Latin America, it was ranked the third most common symptom equivalent to nasal congestion (Meltzer et al., 2012). All spectrum of AR, from mild to severe, suffer from

sleep disturbance. AR manifests all dimensions of sleep complaints (difficulty in falling asleep, nocturnal awakening, early awakening, nonrestorative sleep, feeling of lack of sleep and snoring) and sleep disorders (insomnia, severe insomnia, sleep apnoea syndrome and hypersomnia) (Léger et al., 2006). The resultant impact discovered in a study was nearly half of the AR patients reported feeling of fatigue even though they have seemingly slept normally through the night. Males displayed a higher tendency for sleep apnoea, whilst asthmatic patients correlated with severe insomnia. Similar results were also yielded with a prospective, multicentre Spanish study, 52.8% of patients suffered from poor sleep quality. Nasal congestion and concomitant asthma were the main reasons for poor sleep (Colás et al., 2012). Patients with moderate to severe AR spectrum were most affected from sleep deprivation.

Fatigue due to sleep deprivation contributes to a poorer quality of life for AR sufferers. Daytime somnolence is a marked characteristic of AR. Daytime somnolence is associated with a significant decline of psychomotor skills, lowered cognition and defective learning. About 40% of parents interviewed in a US survey for 500 children with nasal allergies reported nasal allergies interfered with their child's performance at school and more than half of the group had difficulty with performing work or other activities or accomplishing less (Derebery, Meltzer, & Boyle, 2008). The ripple effect of prolonged fatigue could lead to stress and increase the risk of depression (Léger et al., 2006).

2.6.3. Stress and anxiety

The effects of stress and anxiety as a result of sensitisation correlate with AR comorbidities or vice versa. Individuals suffering from AR, displayed a higher level of emotional reactivity such as irritability, mood swings and anxiety when compared to non-AR (Bedolla-Barajas, Morales-Romero, Pulido-Guillén, Robles-Figueroa, & Plascencia-Domínguez, 2016). Experimentally-allergen-induced *in vitro* models demonstrated increased activities of Th2 cytokines and

corticotrophin-releasing factor with a peptide hormone and a neurotransmitter generally released during stress responses, in the prefrontal cortex (Tonelli et al., 2009). The proposition was a causal link between allergen sensitisation and elevated activity of anxiety in the brain function. Two-fold increases in pro-Th2 cytokines IL4, IL5 and IL13 in prefrontal cortex indicated neural responses in allergic reactions. The authors speculated the involvement of T-cells and corticotrophin-releasing factor could be associated with the higher stress responses in AR sufferers. The level of stress experienced in patients also correlated with the severity of AR. Patients with intermittent AR on the severity scale of moderate to severe tended to experience higher significant stress than mild AR sufferers (K. Lee et al., 2008). Negative parameters in Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), a quality of life measure demonstrated strong correlations with fatigue and stress (Park, Shin, Lee, Cho, & Kim, 2012). With amplified stress and anxiety in AR patients, the risk of depression poses a high risk factor. A longitudinal study in adolescents with AR showed a higher prevalence of major depression in later life and onset of any depressive disorder (M. H. Chen et al., 2013). However, the neural mechanism and allergic pro-inflammation causing depressive disorder in AR are still yet to be explored in its entirety.

2.7. Classifications of AR

2.7.1. Seasonal AR and perennial AR

AR was traditionally classified as seasonal AR (SAR) and perennial AR (PAR) by ARIA and is still in currency. J. Bousquet et al. (2001) reiterated that the classification of AR has always been based on the time of exposure. SAR is associated with the exposure of outdoor allergens, in particular, pollens or moulds while PAR is linked to indoor allergens exposure such as dust mites, insects and animal danders. A comprehensive data from Allergies in America, Pediatrics Allergies in America, Allergies in Latin America and Allergies in Asia Pacific based on telephone survey noted that 56% of US adults suffered from PAR while 43% suffered from

SAR, one half of the US respondents experienced AR symptoms for more than four months in a year, with one in five patients experienced AR symptoms more than nine months in a year (Meltzer et al., 2012).

On the contrast, both Latin America and Asia Pacific adults tend to have a higher prevalence of SAR sufferers (61% and 63% respectively). The remaining 1% (US), 2% (Latin America) and 4% (Asia Pacific) respondents cited not knowing the types of AR they suffered from (Figure 5).

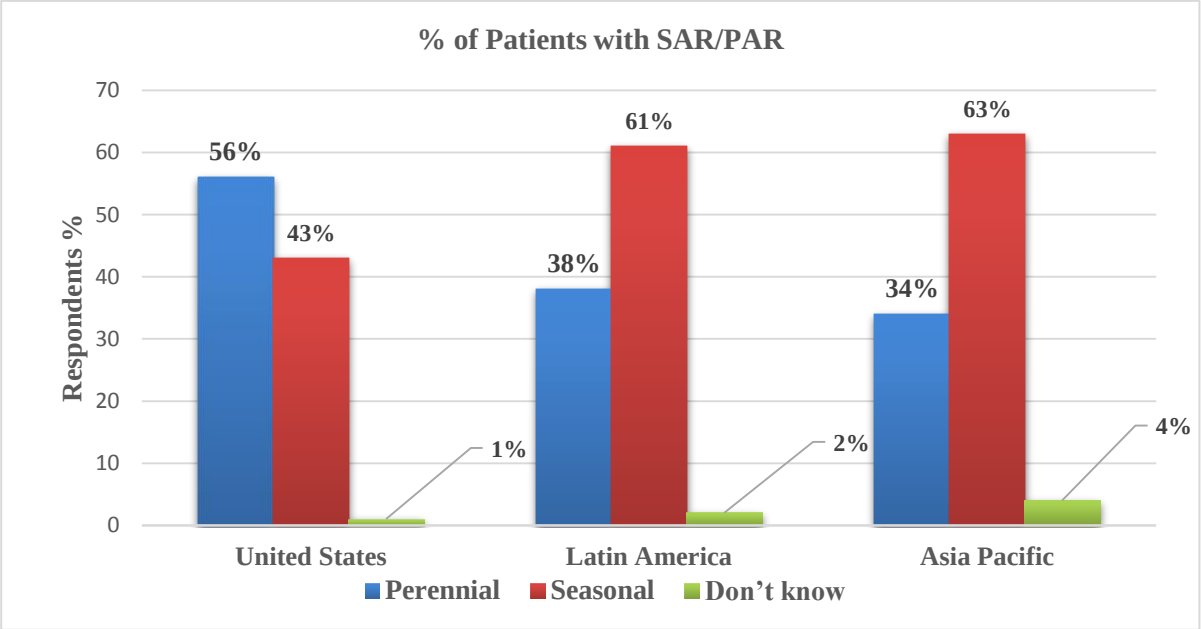


Figure 5. Percentage of respondents suffering from SAR and PAR globally (extracted from Figure 1C on page S117 of Meltzer et al, 2012)

2.7.2. Intermittent AR (IAR) and Persistent AR (PER)

ARIA proposed an additional subdivision of intermittent AR (IAR) and persistent AR (PER) to the existing traditional classification of seasonal AR (SAR) or perennial AR (PAR) in 2001 (J. Bousquet et al., 2001). The objective of this classification provide a guideline for differentiating the duration and severity of AR. Recognising the symptomatic disorders of AR is of a spectrum, this inflammatory disorder is also classified as mild or moderate-severe depending on the

severity of the symptoms and on the quality of life outcomes (J Bousquet et al., 2008; J. Bousquet et al., 2001) (Table 4). J Bousquet et al. (2008) acknowledged in ARIA 2008 update that IAR and PER cannot be used interchangeably with SAR and PAR. The later and the former classification cannot be used in the same stratum of the disease.

Table 4. Nomenclatures of AR classifications according to spectrum of severity (J. Bousquet et al., 2001)

Spectrum of AR	**Classifications of AR**
Intermittent	"Intermittent" means that the symptoms are present: Less than 4 days a week; or For less than 4 consecutive weeks
Persistent	"Persistent" means that the symptoms are present: More than 4 days; and For more than 4 consecutive weeks
Mild	"Mild" means that none of the following items are present: Sleep disturbance Impairment of daily activities, leisure and/or sport Symptoms present but not troublesome symptoms
Moderate to Severe	"Moderate to severe" means that one or more of the following items are present: Sleep disturbance Impairment of daily activities, leisure and/or sport Impairment of school or work Troublesome symptoms

The objective of the new classification was put forth to aid practising physicians with administration of the pharmacologic treatments according to the spectrum of severity and patient's quality of life affected by the disease. However, this new classification is encumbered with complexity for practising physicians and does not yield significant improvement nor translate to a difference in therapeutic options (J Bousquet et al., 2008). Therefore, it is common for physicians to still rely on the traditional AR classification in differentiating and administrating therapeutic options for AR patients.

2.8. Diagnosis of AR

Initial physical diagnosis of AR has to be differentiated from other respiratory symptoms which may appear similar to AR. AR symptoms are mainly attributed to IgE specific allergens and physical examination are recommended to eliminate other non-allergic causes of nasal obstruction and rhinorrhoea that may be related to infections, tumours or other chronic inflammations (Seidman et al., 2015).

2.8.1. AR symptoms

AR is characterised by several symptoms mainly nasal symptoms, ocular symptoms, otic symptoms and systemic symptoms. Nasal symptoms involve repeated sneezing, nasal congestion, itchy nose, runny nose and postnasal drips. Ocular symptoms involve itchy eyes, crimson eyes, excessive tearing and puffy eyelids. Otic symptoms may include pain in the ear, itchy ears, pressure in the ear and constant blockage of the ear. While systemic symptoms can be widely ranged from sleep disturbance, extreme fatigue, anxiety and general poor health. Immunologically, *in vitro* results demonstrated early phase reaction of AR is marked by repeated sneezing and itching of the nose that may last more than one hour, while late phase reaction of AR manifested nasal congestion that persisted for three to 11 hours (D. Y. Wang & Clement, 2000).

Nasal congestion was the main symptom cited by AR sufferers in the US to have the most impact during their worst month. However, in respondents in Asia Pacific, sleep disturbance was cited as the most common during their worst month (Meltzer et al, 2012) (Figure 6). In contrast to a recent clinical practice guideline established by the American Academy of Otolaryngology – Head and Neck Surgery on the types of symptoms for accurate diagnosis of AR (Seidman et al., 2015), it appeared that AR sufferers bore symptoms beyond nasal, otic and ocular ailments.

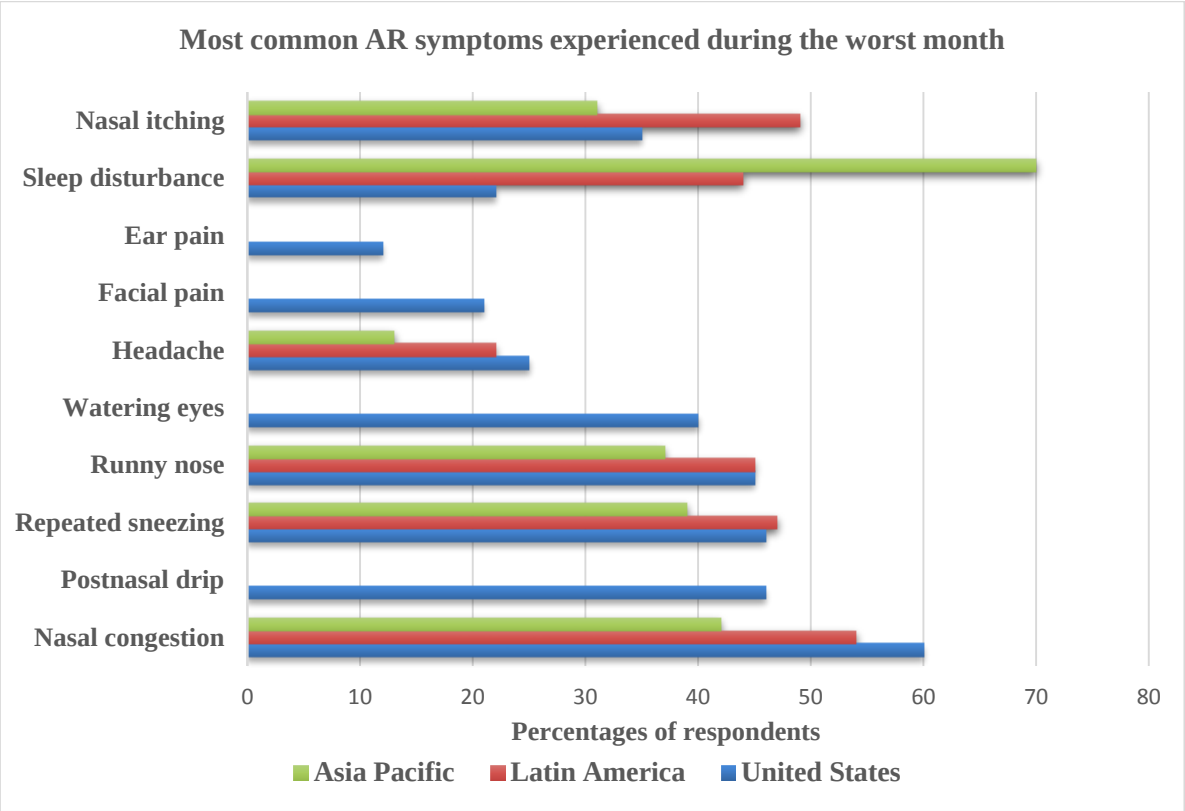


Figure 6. Most common AR symptoms experienced during respondents' worst month in Asia Pacific, Latin America and United States (data extracted from Figure 3 on page S119 of Meltzer et al, 2012)

2.8.2. Ear, Nose and Throat (ENT) examination

Physical ENT examination was highly recommended hand in hand with empirical treatment without first subscribing allergy testing (Seidman et al., 2015). Historical and physical findings of signs and symptoms as well as stimuli and exposure could potentially point to whether findings fit AR signs (Table 5). While empiric treatment could be subjected to the ARIA guidelines of diagnostic algorithm based on the severity of the symptoms (Figure 7), confirmatory allergy testing could be the next step for clinicians to follow up if empiric treatment fails. The role of patient preferences on costs, risks and benefits and the types of testing in shared decision with the clinician is an upmost consideration. In taking these recommended steps, costs of burden to healthcare system and individuals could be substantially reduced.

Table 5. Historical and physical ENT findings in AR (Seidman et al., 2015)

Presenting Symptoms	**Historical Findings**	**Physical ENT Findings**
Nasal congestion	Seasonal or perennial nature of symptoms	Clear rhinorrhoea – clear or coloured (coloured rhinorrhoea may indicate comorbid disease with AR) Bluish or pale swelling of nasal mucosa
Sneezing	Symptoms on exposure to particular agent (animals, particular plants)	
Rhinorrhoea - clear or coloured (coloured rhinorrhoea may indicate comorbid disease with AR)	Family history of atopic or allergic disease Current medications	
Itching of eyes, nose and palate	Symptoms on exposure to irritants (makes allergic origin less likely)	Ocular findings (watery discharge, swollen conjunctivae, scleral injection) Ocular findings (watery discharge, swollen conjunctivae, scleral injection) Allergic shiners Nasal crease
Postnasal drips **Frequent throat clearing** **Cough**	Symptoms of respiratory infection (makes allergy origin less likely)	Frequent throat clearing
Malaise (may be presented with complaints in children) **Fatigue (may be presented with complaints in children)**		Absence of foreign body, tumour, purulence suggesting infection

(Dazaley, 2015)

Step 1. Mild symptoms (intermittent)

- Intranasal
- H_1 blockers plus decongestants or
- Decongestants only
- Anti-leukotrienes

Step 2. Moderate to severe symptoms (intermittent)

- Similar to Mild (intermittent treatment) plus glucocorticosteroids or cromones

Step 3. Mild symptoms (Persistent)

- Review after 2 to 4 weeks for improvement or failure

Step 4. Moderate to severe symptoms

- Intranasal glucocorticosteroids
- H_1 blockers
- Anti-leukotrienes
- Successful – step down treatment to Step 3.
- Failure – review
- Review
  a) Add or increase glucocorticosteroids
  b) If rhinorrhoea, add ipratropium
  c) If nasal blockage, use decongestant or short term dose of glucocorticosteroids
  d) Conjunctivitis – use oral or intraocular H_1 blocker or intraocular cromones or saline
- Failure – refer to specialist
- Consider immunotherapy

Figure 7. Algorithm for the diagnosis and management of AR (data adapted from page 5 of J. Bouquet.et al. 2007)

2.8.3. Allergen specific tests

IgE testing is conducted in either blood or skin. The following types of IgE-specific tests are listed in Table 6. The most commonly used forms of IgE specific tests are skin prick test and intradermal dilution.

Table 6. Types of allergen specific tests (Seidman et al., 2015)

Allergen specific testings	**Specificity**
Skin prick-IgE	High specificity and sensitivity, commonly used; Contraindicated in skin diseases
Scratch testing-IgE	Reduced specificity and sensitivity, with poor reproducibility, rarely used; Contraindicated in skin diseases
Intradermal/ intradermal dilution	Specific allergen identification of allergen sensitisation, commonly used and highly sensitive; Contraindicated in skin diseases
Provocation neutralization test	Historical interest for inhalant allergy testing; No clinical correlation and immunologic mechanism are established for this testing
ImmunoCAP-IgE	High specificity for anti-IgE antibodies affixed to radioactive tags; High sensitivity for specific allergen and costly
Acoustic rhinometry	Non-specific for IgE
Olfactory testing	Non-specific for IgE
Microarray testing	Non-specific for IgE
Nasal nitric measurements	Non-specific for IgE
Nasal smears	Lacks accuracy and sensitivity

Skin testing detects sensitisation to the mast cells reactivity owing to the presence of IgE. Wheals and flares are formed when epithelial mast cells interacts with the antigen. Where skin testings are contraindicated, *in vitro* methods using the patient's serum are tested for allergy sensitisation. For radioallergosorbent test (RAST), the term "radio' should no longer be used, as the assays used currently no longer contain radioactive material (Pudupakkam, 2014). Currently, ImmunoCAP is a popular choice of *in vitro* diagnosis with high binding specificity for allergen testing.

2.9. Management of AR

For the AR sufferers, there are three levels involved in the management of AR namely; primary, secondary and tertiary (J Bousquet et al., 2008).

The primary level of management involves personal and community wide efforts to enforce good levels of physical fitness, nutrition and emotional wellbeing. Steps should be taken to enhance the level of self-immunity through means of immunisation to prevent infectious diseases. The secondary level includes early detection of AR symptoms and effective measures to prevent exacerbation of sensitisation when physical evidence emerges. Education in avoidance of allergen is highly recommended for AR sufferers. Last, the tertiary level involves measures to eliminate long-term impairments of AR (J Bousquet et al., 2008). When AR persists, despite steps taken at both primary and secondary levels, the use of pharmacotherapy comes into place.

For the clinical physicians, poor diagnosis of AR is often met with inadequate or inaccurate therapies leading to poor treatment outcome. An algorithm for the management of AR was developed by ARIA to aid the family physician in diagnosis and prescription of medications. Severity spectrum of AR has to be taken into considerations whether the symptoms were mild or moderate to severe. First, for intermittent mild AR symptoms, oral, intranasal anti-histamines or combined anti-histamines with decongestant would be prescribed. Second, for intermittent moderate to severe AR symptoms, anti-leukotrienes antagonists may be prescribed. If the symptoms persisted after two to four weeks, a step up management would be considered. PER symptoms, ranging from moderate to severe would be reviewed after the first line of pharmacotherapy. At this level, glucocorticosteroids, cromones and anticholergenics would be prescribed. Finally, when all have failed to deliver relief of AR, immunotherapy would be in place as the last line of pharmacotherapy for severe PER.

2.9.1. Allergy avoidance and education

The ARIA guidelines advocated allergen avoidance and education as one of the strategies for AR management (J. Bousquet et al., 2001). Avoidance of allergens was strongly recommended with the interventions in lifestyle. AR sufferers with pollen allergies might encounter pollen challenge on an annual basis; however, the magnitude of the exposure to allergies may be more extensive. Taking the extra steps to avoid immediate exposure to the risk of allergen specific induction could relieve the symptoms (Table 7).

Table 7. Strategies for reducing allergens according to ARIA (J. Bousquet et al., 2001)

Types of allergens	**Strategies of reducing allergens**
Indoor allergens	• Seal mattress, pillow and duvet in mite allergen impermeable casing • Wash beddings in hot water (> 50°C) weekly or dry laundry in sun to terminate mites • Wash laundry in cold water to reduce dust allergen • Remove wall to wall carpet • Steam clean with liquid nitrogen or acaricides to reduce mite numbers in carpet if it cannot be removed • Wash curtains at 55°C • Wash in hot water (55°C), freeze or remove children's soft toys • Use acaricide sprays to reduce allergens • Use high efficiency particulate air vacuum cleaners and double thickness bags • Reduce humidity levels in the home and install effective ventilation systems or ensure aeration for adequate ventilation • Repaint and treat mouldy dwellings • Restrict or remove pets in lodgings
Outdoor allergens	• Wear protective masks and eyeglasses • Seal the lodging by day and aerate only at night when pollen load is high

Education of AR involves the use of the medications prescribed to AR patients, with the most common form being oral and intranasal. The right administration for the severity of AR and duration are crucial for the increase responsiveness to the right medications. Patient's compliance, physician's right diagnosis and prescription will greatly increase efficacious outcome on AR symptoms.

2.9.2. Pharmacotherapy for AR

The mainstream pharmacotherapy for AR is well established with many options of relief for AR sufferers. The options of these pharmacotherapies depend on the severity and the duration of AR experienced by the patients and the physicians in care to accurately dispense the right medication for the treatment.

i. Anti-histamines

Anti-histamines are also known as H_1 receptor antagonists, H_1 blockers or oral H_1. Anti-histamines primarily act on selective histamine receptors and there are four subtypes of histamines receptors: H_1, H_2, H_3 and H_4. H_1 and H_2 receptors are commonly expressed in the human tissues, whereas H_3 and H_4 are limited. The former are abundant in skin, intestinal mucosa and respiratory tract, while the latter H_3 are found throughout the nervous system with H_4 receptors in the thymus, small intestines, spleen, colon, bone marrow and basophils. Histamine release is triggered by antigenic binding of IgE specific allergens. Histamine release causes both acute and systemic hypersensitivity reactions manifested in AR symptoms. The pharmacologic rationale of these anti-histamines targets inflammatory mediators associated with AR such as ECP, granulocyte-macrophage colony-stimulating factor (GM-CSF), histamine, intracellular adhesion molecule 1 (ICAM-1), interleukin (IL) 1β (ILl-β), IL6, IL8, kinins, myeloperoxidase, nuclear factor kappa beta (NF-κβ), nitric oxide (NO), substance P, TLR 3, tryptase and tumour necrosis factor-α (TNF-α) (Hernandez-Trujillo, 2009). In spite of their efficacy in downregulating the AR mediators, there remain many side effects of these anti-histamines (Table 8.).

Table 8. Modes of administration, action onset and side effects of anti-histamines for AR (J. Bousquet et al., 2007; Cassell & Katial, 2009)

Generic names of anti-histamines	Modes of administration	Action onset	Side effects
Cetrizine (Zyrtec)	Oral	1 hour	• Sedation • Mucosal dryness • Urinary retention
Ebastine		<1 hour	• Drowsiness • Headache • Dry mouth • Pharyngitis • Indigestion • Nausea • Epistaxis
Levocetirizine (Xyzral)	Oral	1 hour	• Sedation • Mucosal dryness • Urinary retention
Fexofenadine (Allegra, Telfast)	Oral	1 hour	• Headache
Loratadine (Claratin, Alavert)	Oral	3 hours	• Sedation with higher dosages
Desloratadine (Clarinex, Aerius)	Oral	2.5 hours	
Olopatadine (Patanase)	Intranasal	30 minutes	• Bitter taste • Epistaxis • Somnolence • Headache
Levocabastine (Livostin)	Intranasal, intraocular	<1 hour	• Visual disturbance • Dry mouth • Fatigue • Pharyngitis • Eye pain • Dryness • Somnolence • Cough • Nausea • Rash • Dyspnoea
Azelastine (Astelin, Astepro)	Intranasal	15 minutes	• Bitter taste • Epistaxis • Somnolence • Headache
Azelastine olus Dymista (fluticasone)	Intranasal		
Rupatadine	Oral		• Somnolence • Headache • Fatigue

ii. Glucocorticosteroids

Glucocorticosteroids (Glu) is an immunosuppressant, categorised as a class of steroids hormones. This class of drugs is generally used as the first line therapy for moderate to severe PER. The anti-inflammatory mechanism of Glu is distinct. Glu targets glucocorticoid receptors and its ligand-binding affinity with chaperone molecules on cell membrane. Its activity is mainly distinct in its action on the translocation to the nucleus where it activates transcription of anti-inflammatory genes and destabilises the pro-inflammatory mRNA species (Barnes, 2010; Baschant & Tuckermann, 2010). Its transcriptional inhibition extends to components such as activator protein-1, NF-κβ, interferon regulatory factor-3 (IRF-3), signal transducer and activator of transcription (STAT), cAMP response element binding (CREB) protein, nuclear factor of activator T-cells (NFAT), T-box transcription factor (T-bet) and trans-acting T-cell-specific transcription factor GATA-3, all are pro-inflammatory transcription factors that regulate transduction of inflammation cascade of cytokines (Baschant & Tuckermann, 2010). Intranasal Glu are generally effective on nasal congestion. When comparing administration of Glu in terms of oral to immunotherapy; the latter should only entail a short duration. This is due to its systemic side effects that are associated with its immunosuppressive nature (Table 9).

Table 9. Modes of administration, action onset and side effects of glucocorticosteroids (J. Bousquet et al., 2007; Moghadam-Kia & Werth, 2010)

Names of glucocorticosteroids	**Modes of administration**	**Action onset**	**Side effects**
Beclomethasone diproionate **Budesonide** **Ciclesonide** **Flunisonide** **Fluticasone propionate** **Fluticasone furoate** **Mometasone furaote** **Triamcinolone acetonide**	Intranasal	6 to 12 hours, maximal effect after a few days	• Suppresses wound healing
Dexamethasone **Hydrocortisone** **Methylprednisolone** **Prednisolone** **Prednisone** **Triamcinolone** **Betamethasone** **Deflazacort**	Oral/ Immunotherapy	6 to 12 hours, maximal effect after a few days	• Local tissue atrophy or myopathy • Bone loss resulting in osteoporosis • Hypercalcicuria • Hypertension • Increased osteocytes apoptosis thus resulting in avascular necrosis particularly in the femoral head • Elevation of serum lipids resulting in hyperlipidaemia • Decrease glucose utilisation and increase hepatic glucose production resulting in hyperglycaemia, development of diabetic syndrome • Increase in ischemic heart disease and heart failure • Mood alterations, memory deficit and risk of psychosis • Gastrointestinal (GI) complications such as gastritis, peptic ulcerations, GI haemorrhages and acute pancreatitis.

iii. Decongestants

Decongestants are categorised as sympathomimetic drugs, which are effective in relieving nasal congestion. These drugs are primarily α-adrenergic agonist, targeting on α-adrenergic receptors on blood vessels of nasal mucosa, inducing vasoconstriction which decreases blood flow through the mucosa and shrinks the nasal erectile tissues (McLeod, Erickson, Mingo, & Hey, 2001). α_2-adrenergic receptors are abundant in the nasal mucosa, *in vitro* study on a cat with nasal congestion demonstrated the decongestant effect of α_1-adrenergic agonist phenylephrine, a topical BHT-920 (a selective α_1-adrenergic agonist phenylephrine) and non-selective α-agonist oxymetazoline, all were successful in producing a decongestant effect (McLeod et al., 2001). This study revealed not just the positive outcome of the decongestant but it highlighted the potential adverse effects of the use of sympathomimetic amines. Transient hypertension was associated with oxymetazaoline and phenylephrine, systemic elevation of blood pressure is significantly related to dosage. The real concern is when this class of drugs is prescribed to young children, cardiovascular instability and respiratory depression and sedation could pose potential death (Tobias, Cartabuke, & Taghon, 2014). Abuse of this class of drugs owing to lack of education on the limit of use and the availability as OTC drugs could present cardiovascular risk and rhinitis medicamentosa due to rebound hypertrophy of nasal mucosa. The side effects of the sympathomimetics are summarised in Table 10.

Table 10. Modes of administration, action onset and side effects of decongestants (J. Bousquet et al., 2007)

Names of decongestants	**Modes of administration**	**Action onset**	**Side effects**
Ephedrine	Oral	15 to 30 minutes	Minor effects include • Nausea • Vomiting • Headache • Dizziness • Dry mucosa Serious effects include • High blood pressure • Palpitations • Restlessness • Urinary retention • Seizures • Insomnia • Exacerbation of glaucoma • Thyrotoxicosis Rhinitis medicamentosa if used > 10 days • Hypertension Stroke

iv. Anti-leukotrienes

Anti-leukotrienes are designed as mediators-specific antagonists to target cysteinyl leukotrienes (cysLTs). These are primarily inflammatory lipid mediators deriving from lipoxygenase pathway of arachidonic acid cascade (Abbas et al., 2012). LTC_4, LTD_4 and LTE_4 are implicated in the pro-inflammatory responses in mast cells proliferation, monocytes and macrophages migration and production of reactive oxygenated species (ROS), eosinophilic migration and adhesion to vascular endothelium, increase in cytokines IL10 and IL8 in dendritic cells and neutrophils proliferation with NO production. Interaction with these cysLTs commonly produced responses of chronic AR or late phase reaction in AR as well as in asthma with manifestations of bronchial hyperresponsiveness, airway constriction, oedema, excess mucous secretion and increased airway resistance (Rosenwasser, 2007). Anti-leukotrienes such as montelukast, pranlukast and zafirlukast target neutrophils, monocytes and macrophages by inhibiting multi anti-inflammatory targets, namely; arachidonate 5-lipoxygenase cataclysm to

LTE_4, production of reactive oxidative species (ROS), NF-κβ transcription, Prostaglandin E_2 (PGE_2) synthase and cyclic nucleotide phosphodiesterases which subsequently increase 3′5′-cyclic adenosine monophosphate (cAMP), a pro-inflammatory regulator in innate immunity (Theron et al., 2014). Table 11 summarises the modes of administration, action onset and side effects of anti-leukotrienes.

Table 11. Modes of administration, action onset and side effects of anti-leukotrienes (J. Bousquet et al., 2007)

Names of anti-leukotrienes	**Modes of administration**	**Action onset**	**Side Effects**
Montelukast	Oral	Rapid	• Headache • Gastrointestinal • Nausea • Fatigue • Fever • Mild rash
Pranlukast			
Zafirukast			Serious side effects include • Exacerbation of asthma • Respiratory exacerbation • Mood changes • Anxiety • Insomnia • Depression • Severe tingling sensation in extremities • Skin rash • Bruising • Muscle weakness or atrophy

v. Anticholinergics

Anticholinergics are antimuscarinic agents which produce bronchodilation in the smooth muscle of the airways. Elevation of airway resistance attributed to the increased vagal tone of the cardiovascular and respiratory systems is commonly associated with moderate to severe AR and asthma. Anticholinergics mainly act on the muscarinic receptors namely M1 receptors (commonly found on cholinergic ganglia), M2 receptors (found on postganglionic fibres) and M3 (found on smooth muscles, mucosa and vascular endothelium) (Novelli, Malagrinò, Dente, & Paggiaro, 2012). The target is to restrict the release of neurotransmitter acetylcholine mediating through the parasympathetic pathway. The administration of this class of drug is mainly by use of a nebuliser and its effects are known to be short lasting; however, this drug is not without its side effects (Table 12).

Table 12. Modes of administration, action onset and side effects of anticholinergics (J. Bousquet et al., 2007)

Names of anticholinergics	**Modes of administration**	**Action onset**	**Side effects**
Ipratropium bromide	Intranasal	Rapid	Mild effects include • Dry mouth • Blurred vision • Constipation • Drowsiness Serious effects include • Memory impairment • Exacerbation of glaucoma • Prostatic hypertrophy

vi. Cromones

Cromones are also known as disodium cromoglygate, cromolyn sodium, cromoglygate, and cromolyns. Aside from the myriad names, this class of drugs is commonly termed as mast cell stabilisers. Cromones had been advocated to be administered prophylactically in order to achieve its maximum effect. The mechanism of cromones promoted the activation of protein kinase C phosphorylation and secretion of Anx-A1, an annexin peptide that possessed

inhibitory action on histamine-release and prostaglandin 2 (PGD_2) anti-inflammatory cascade in mast cells (Yazid, Sinniah, Solito, Calder, & Flower, 2013). This study also discovered that chromones yielded variable effects only when there was an absence of the late phase reaction *in vitro*. This could explain that the timing of cromones administration is highly crucial for it to exert its full effects, although the mechanism is not fully known. Table 13 summarises the key types of cromones, their modes of administration, action onset and side effects.

Table 13. Modes of administration, action onset and side effects of cromones (J. Bousquet et al., 2007)

Names of Cromones	**Modes of administration**	**Action onset**	**Side effects**
Sodium cromoglycate	Intranasal/ intraocular	6 to 12 hours, maximal effect after a few days	• Short lasting effects for intranasal • Administered before allergen exposure season for full effects • Excellent safety therapy
Nedocromil sodium			
Naaga			

2.9.3. Allergen specific immunotherapy

For severe PER or PAR, allergen specific immunotherapy is the last option when all Western pharmacotherapies have been exhausted. Allergen specific immunotherapy is a treatment process which involves repeated administration of specific, semi-purified allergen extracts with the aim of reducing symptoms on subsequent allergen exposure, improving quality of life and inducing long-term tolerance to a "naturalised" adaption of allergen exposure (Walker et al., 2011). Several factors are considered before allergen specific immunotherapy is introduced to AR sufferers including patient's receptiveness, adherence, medication requirements, reaction to avoidance measures, AR and asthma exacerbation, affordability and allergy triad manifestations (AR, asthma and atopic dermatitis).

There are two routes of administration for allergen immunotherapy treatment namely; subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT). As the term

denotes, SCIT is a specific purified allergen injection administered under the arm on an incremental dose. The objective is to achieve a Th2-Th1 shift immunologically with a sustained maintenance dose and this regime is continued for at least over a period of two years. SLIT is an alternative approach where the course of immunotherapy regime is administered with a tablet or spray under the tongue. This mode of immunotherapy is generally dispensed for children with severe AR or atopic diseases.

A comparative study measured the clinical efficacy of SCIT, SLIT and pharmacotherapy over a period of one year utilising two species of dust mites *Dermatophagoides pteronyssinus* and *Dermatophagoides farina* antigenic immunotherapy. Although results indicated effects of SCIT and SLIT decreased the specific allergen reactivity in skin and increased the threshold to induce nasal hyper-reactivity in VAS, however variable analysis on allergen-induced cytokine IL10 was reflected (Eifan et al., 2010). The main role of IL10 is to inhibit further differentiation of Th1 cells and macrophages activation. It has an important role in turning off the T-cells activation as well as inhibitory effects on mast cells and basophils in adaptive response. Therefore IL10 is inextricably linked to down-regulation of mast cell inflammatory release in the nasal mucosa (Abbas et al., 2012). In this study, an observable increase in the IL10 was discovered with SLIT even though AR symptoms were reduced. Increase in rescue medication (anti-histamine, intranasal/inhaled/oral corticosteroids and β2 agonists) usage in SLIT and non-significant titrated IgE levels also did not seem to correspond with the reduction of nasal symptoms reflected on VAS. Two systemic adverse events relating to SCIT emerged with flushing, wheezing and dyspnoea bordering on the risk of anaphylaxis required adrenaline treatment.

Variable results of the peripheral blood mononuclear cells of AR patients *in vitro* were also rendered on IL10 in comparison with AR symptoms for SCIT, indicating greatest reduction of

AR symptoms corresponded with the least increase of IL10 expressions, while greatest increase of IL10 was detected in patients with the least reduction in AR symptoms (Savolainen, Laaksonen, Rantio-Lehtimaki, & Terho, 2004). The authors purported that early or transient increase in IL10 and IL18 mRNA expression was crucial to yield beneficial outcome in SCIT. However, it appears that this phenomenon is also visible in SLIT in the previous discussion. Clearly, the role of IL10 and correlation of symptoms attenuation require further exploration in immunotherapy studies. R. Pawankar, Canonica, et al. (2011) acknowledged that clinical studies on immunotherapies had produced heterogeneous results, of which led to weak meta-analyses.

A four-year retrospective German survey investigated on the long-term effectiveness, local reactions and systemic reactions of SCIT (venom or inhaled allergen immunotherapy) on a cohort of 1,257 patients with AR, conjunctivitis, allergic asthma and stinging insect hypersensitivity in a clinical study. Its results showed that overall systemic reactions prevalence was 13.6% (n = 195), while local reactions prevalence was at 13.9% (n=175). The major risk of immunotherapy was anaphylaxis (Adamic et al., 2009). Furthermore, a SR evaluating effectiveness of SCIT for allergic rhinoconjunctivitis and asthma indicated 35 out of 61 included SCIT studies reported safety data. Out of 35 trials, 13 anaphylactic reactions were reported in four trials which involved 205 participants (Erekosima et al., 2014). Common local reactions associated with immunotherapy included itching and swelling of nodules, swelling of lips and rashes while systemic reactions were urticaria, rhinoconjunctivitis, oral allergy syndrome and asthma (Winther, Malling, & Mosbech, 2000). This study also indicated unspecific symptoms such as tiredness, headache and malaise would emerge after immunotherapy. Despite the side effects and heterogeneous results of meta-analyses of the reviews on immunotherapies, immunotherapies treatment still yielded efficacious outcomes on the reduction of nasal allergy symptoms.

2.9.4. Complementary and alternative medicine (CAM) for AR

CAM refers to any therapeutic interventions that exist outside conventional medicine and are used interchangeably with traditional medicine in some countries (Kern & Bielory, 2014; WHO, 2013). The WHO (2013) further defined CAM as a broad set of healthcare practices that are not integrated into the mainstream healthcare system. In Australia, the rising demand of CAM was reflected in a telephone-based survey carried out in 2005. Findings revealed that 44.1% of Australian adult respondents visited a CAM practitioner, estimated 69.2 million of visits during the 12-month period (C. C. L. Xue, Zhang, Lin, Da Costa, & Story, 2007). Varied forms of CAM for AR are available for AR such as acupuncture and CHM in CM.

The foundation of CM is a unique system of medicine based on written texts that long existed since the second millennium (Maciocia, 2008). These written texts provide fundamental knowledge in CM clinical practice. Comprehensive notation of the clinical treatments and pharmacopoeias in genres of CM classical literature highlights effective treatments of myriad of diseases that still pose a challenge in healthcare today. The WHO acknowledges demands for CM correspond with an increasing dissatisfaction with existing healthcare services, an increasing awareness of options in healthcare and an interest in individualised care and disease prevention associated with CM (WHO, 2013). Modalities used in CM include acupuncture, ear acupuncture and/or ear acupressure, and CHM.

2.10. Comments

The interventions for AR are extensive and well established. Drug treatment is regarded as the mainstream pharmacotherapy intervention for AR in ARIA Guideline 2008 update (J Bousquet et al., 2008). However, there is a distinct gap in the regard of long-term efficacy and systemic side effects of AR pharmaceuticals drugs.

Mahr, Sheth, and Boyle (2008) raised the concern of a lack of efficacy of intranasal corticosteroids for long-term relief of symptoms reported by parents in children with AR from five to 17 years based on a telephone survey conducted by the Pediatrics of America. A total of 31% reported loss of efficacy within four to seven hours of administration, 89% indicated loss of efficacy within 24 hours and 54% cited attenuated effects in the medication. Side effects attributed to the nasal sprays were post nasal drips (42%) and bad taste (38%) (Mahr et al., 2008). Side effects such as headache, gastrointestinal symptoms, rash and Churg-Strauss syndrome are often associated with intranasal corticosteriods (Greiner et al., 2012).

The availability of OTC drugs further indicates a high chance for abuse of medication. One cross-sectional study employed study of individuals self-medicating persistent rhinitis with intranasal decongestants. Overuse of intranasal decongestant was as high as 49%, even though 80% of the patients were educated about the limitation of use (Mehuys et al., 2014). Frequent use of intranasal decongestants is associated with rebound nasal congestion on withdrawal resulting in hypertrophy of the nasal mucosa known as rhinitis medicamentosa. It is clinically characterised by nasal congestion without rhinorrhoea, postnasal drip or sneezing. Patients with AR comorbid nasal polyposis suffer from rebound vasodilation, oedema, and haemorrhages during nasal intraoperation (Mehuys et al., 2014; Robison, Pant, & Ferguson, 2010). Discontinuation of use of nasal decongestants is often accompanied with withdrawal syndromes such as headaches, restlessness and anxiety (Ramey, Bailen, & Lockey, 2006). Although mainstream pharmacotherapy is well established and researched, permanent resolution of AR symptoms is still unavailable to sufferers. The issues of the side effects of these medications still present a confounding challenge to AR sufferers leaving many to weigh out the risk and benefit ratio to adopt a suitable medication regime for the management of AR. This could potentially pose medication abuse, lack of education in administration, failures in the

medication regime as well as risks and sequelae arising from the complications of the AR therapies. This has prompted a rising demand to seek CAM for the management of AR (G. Hu & Walls, 2005).

The recognition of acupuncture as a form of modality was endorsed by 103 out of 129 countries in the global survey conducted by WHO in 2012 (WHO, 2013). The significant progress of acupuncture is likely attributed to the many clinical trials such as A. R. Kim, Choi, Kim, Jung, and Choi (2011) and Brinkhaus et al. (2013) that were undertaken in the universities throughout the Eastern and Western hemispheres. Acupuncture was recommended by the American Academy of Otolaryngology – Head and Neck Surgery Foundation as an alternative option for AR sufferers seeking non pharmacologic solution for their ailments (Seidman et al., 2015).

In the same vein, many experimental studies have been conducted research on CHM for the management of AR and the results had yielded successful outcomes. It is important to stress that the use of CHM is not a single-herb administration for clinical treatment, it composes of mixture of multiple herbs formulation based on classical understanding of the properties of the herbs to address ailments. Many experimental studies have generated successful outcomes on the effects of AR management such as Nagai et al. (2004), Xu, Liu, Dai, and Zhou (2012) and Kao, Lin, Hsieh, Hsieh, and Lin (2001). Similarly, many clinical trials were also carried out over the years. Majority of the clinical trials and experimental research on CHM were carried out in Eastern hemisphere such as China, Japan, Taiwan and Korea. In fact, a few research on CHM for the management of AR were carried out at universities in the Western hemispheres such as a clinical trial on *Astragali Radix* on AR conducted by the Children's Hospital Srebrnjak in Croatia (Matkovic et al., 2010) and Zurich University of Applied Sciences in Switzerland on toxicities of *Asari Radix et Rhizoma* (C. Chen, Spriano, Lehmann, & Meier, 2009). Access to language as well as classical texts, knowledge of the Chinese Materia Medica, and the cultural

context of CM limit the extent of research in CHM. Hence, it is in the interest of this thesis project to present and collate synthesised reviews on the outcomes of the classical texts data-mining and clinical trials of AR.

Chapter 3 Literature review on AR – A Chinese medicine perspective

This chapter reviews the diagnostic principles of AR from the perspective of CM and the use of CHM as well as other modalities in CM for the management of AR.

3.1. Physiological mechanisms in CM

The terminology “allergic rhinitis” [Guo Min Xing Bi Yan, 过敏性鼻炎] does not exist in Chinese medical annals. Owing to the direct translation of the terminologies and the conceptual descriptions of the pathologies of AR from Chinese to English language, the discourse of AR in the concept CM can be confounding. Comprehending the medical framework from a CM perspective requires an understanding of the Chinese culture and its language to better appreciate how CM embraces the notion of Qi, blood, Yin and Yang which regulate the basic physiological mechanism of the human body. A disruption to Qi-blood mechanisms causes imbalance of Yin and Yang and weakens the body system, rendering it susceptible to invading pathogens.

3.1.1. Qi

Qi is the motive force of all physiological processes (Maciocia, 2008). Classified Classic of Viscera (Lei Jing・Zhangxianglei,《类经・脏象类》) describes Qi as the connotative visceral within physiological functions of the viscera, morphology of the organs and resulting in pathological changes that form an interrelation with the wider environment. It is the guiding principle and a core component of the theoretical system of CM in guiding diagnosis, rehabilitation of health and disease prevention. According to CM philosophy, the human body is made up of energetic pathways akin to the Western medicine notion of neural pathway, filled

with intrinsic driving force, known as Qi (pronounced *chee*) (Chon & Lee, 2013). Qi takes on many different forms and at best is transformative. The movement and the transformation of the Qi are crucial to the homeostasis of the body. Qi is deemed to enter and exit the organs, also rise and descend in dispersion or stagnate and gush in a state of disease. In one of the earliest text, the Plain Questions on Pulse Classics (Ling Shu · Jing Mai, 《灵枢 · 经脉》), Qi Bo stipulated that the construct of human is made up by the physiological aspect and the spiritual aspect: the former where Qi and blood is channelled by nutritive and defensive physiologically within the viscera and the latter emotional and mental faculties are attributed to the Heart where the soul is housed (Wang, 1997). Therefore, Qi is regarded as the motive force that dwells physiologically, regulates emotionally and interacts socially with the wider environment.

3.1.2. Blood

Blood is deemed to be produced by the Spleen in CM. The primary function of blood in CM is considered to nourish the body Classic of Difficult Issues, Chapter 22 (Nan Jing • Ershiernan, 《难经 • 二十二难》(Wiseman & Ellis, 1996). Its role is to provide nourishment for the functionality of the five senses, nine orifices, organs, motor function, muscular and skeletal structure of the human body. Abundant blood supply in CM is detectable in ruddy facial colour, fleshy and sturdy muscle tone, supple skin turgor and lustrous hair while poor blood circulation is reflected in pallor facial colour, dry skin turgor, brittle hair, inflexible and rigid muscles tone. The physiological aspect of the Spleen in CM at first glance does not correlate with the Western physiological mechanics. However, one striking similarity stands out that is, both are related to production of blood. In biomedical perspectives, blood production also known as erythropoiesis process takes place in bone marrow whereas the stress erythropoiesis after acute anaemia takes place in the spleen. The spleen harbours a specialised population of non-morphogenetic protein 4-reponsive progenitors derived from bone marrow cells, which differentiates into erythroid units responsible for the growth and signals of spleen erythroblasts (Millot et al., 2010).

Therefore, the CM ancient stance on the Spleen in its role in producing blood to nourish the body is aligned with the mainstream physiological function of the spleen.

3.1.3. Yin and Yang

The concept of Yin and Yang is both an anatomic and a physiologic concept in the theory of CM (Wiseman & Ellis, 1996). Anatomically, the human body is viewed in terms of Yin and Yang. The anterior aspect of the body is regarded as Yin while the posterior aspect of the body is Yang. Physiologically, the five viscera organs pertaining to Yin are Liver, Heart, Spleen, Lung and Kidney and the Yang organs are Gallbladder, Stomach, Intestines, Bladder and the Triple Burner (Wiseman & Ellis, 1996). Both Yin and Yang organs function differently. Maciocia (2008) highlighted Suwen Chapter 5 which aptly described the Yin and Yang organs function: Yin is in the interior and is the material foundation of Yang; Yang is on the exterior and is the manifestation of Yin. An example of this connotation is the Heart. The function of the Heart governs blood and controls the blood vessels (Yin aspect). Here, the blood vessels in CM refer to energetic layers with skin, muscles, sinews and bones (Maciocia, 2008). If the blood circulation is abundant and strong, the complexion of the face would surface as rosy and lustrous (Yang aspect) (Maciocia, 2008). In addition, both characteristics of Yin and Yang are regarded as one of mutual opposition, dependence, consummation and transformation of each entity (Maciocia, 2008). When both characteristics of Yin and Yang maintain an equal balance of physiological function, it is deemed that homeostasis of biologic in health is achieved hence, good health is attained.

3.2. Definition of AR in CM

There is no clear definition of AR in CM as this terminology does not exist in ancient times. However, the understanding of AR stems from the classical medical texts written by eminent doctors of the early days. Descriptions in the classical texts range from elucidation of the pathology of the nasal cavities to diagnosis and treatments.

In Huangdi's Internal Classic (Huang Di Nei Jing, 《黄帝内经》), a key symptom of AR sneezing [Pen Ti, 喷嚏] was also presented in the text, similar to rhinitis-syndrome. In the Miraculous Pivot (Ling Shu, 《灵枢》), the chapter on oral therapy (Kou wen, 口问) further described the mechanism of sneezing as the exuberance of the Yang energy filling the chest which subsequently surface from the nose to cause sneezing reactions (Wang, 1997). The earliest indication of AR-like signs and symptoms in CM lies in the key word "Bi Qiu" (鼻鼽). In Suwen・Pulse Classics《素问・脉解篇》, Bi Qiu is described as a condition accompanied with sneezing, runny nose and nasal obstruction (Wang, 1997).

In the Compilation of Liu He Jian's Six Medical Books (Liu He Jian Yi Xue Liu Shu, 《刘河间医学六书》), clearly described AR sufferers (鼽者) would be encumbered with clear runny nose discharge (R. Hu, 2015). Similarly, the Ming dynasty medical text, the Miraculous Medical Formulary (Qi Xiao Liang Fang, 《奇效良方》) authored by Dong Su during the Ming Dynasty (R. Hu, 2015), also described the nose as the passage of the Lung which clear air passes and the rhythmic rise and fall of the Yin and Yang in tandem with the body's Qi and the humour, the nose is able to maintain even breathing and the physiological function of differentiating smell. It is apparent that descriptions of AR-like signs and symptoms in the classical texts do exist in retrospective diagnosis and are closely associated with modern AR. To date, in CM terminology, "Bi Qiu" is regarded as the closest association to AR.

3.3. Aetiologies

The causes of pathological diseases are attributed to the both internal and external stimuli. External pathogenic factors are the result of exposure to the elements in terms of geographical dwellings or the occupational locality of individuals. These external pathogenic factors consist of wind, cold, summer-heat, damp, fire-heat and dryness. These are climatic factors that affects the immunity of individuals known as Zheng Qi in CM. Internal factors are derived from seven emotions (i.e. anger, joy, sadness, worry, pensiveness, fear and shock) associated with taxation in mental health, nasal injuries or trauma (Maciocia, 2008).

3.4. Pathogenesis of AR

Pathogenesis of AR is highly associated with a dysfunction of three organs namely; Lung, Spleen and Kidney. In the book of Miraculous Medical Formulary, Chapter 59 (Qi Xiao Liang Fang・Juanzhiwushiju, 《奇效良方・卷之五十九》), according to CM description, the Lung is responsible for penetrating arterials for Qi flow. The balance of Ying and Wei is crucial to maintain good health. Wei refers to the defence barrier mechanism in the interstitial spaces of the skin and muscles, while Ying refers to the nutritive Qi that flows in the blood (Maciocia, 2008). Adequate nourishment of nutrients in the blood provides harmony in the Ying-Wei and proper protection from external pathogen would ensure the good physiological functioning of the nose. The nasal pathology in CM fits the description of AR, is linked to the dysfunction of Lung, Spleen and Kidney when either internal or external factors attack the organs and the nose or vice versa. The interplay of these organs is shown in the pathogenesis diagram below (Figure 8).

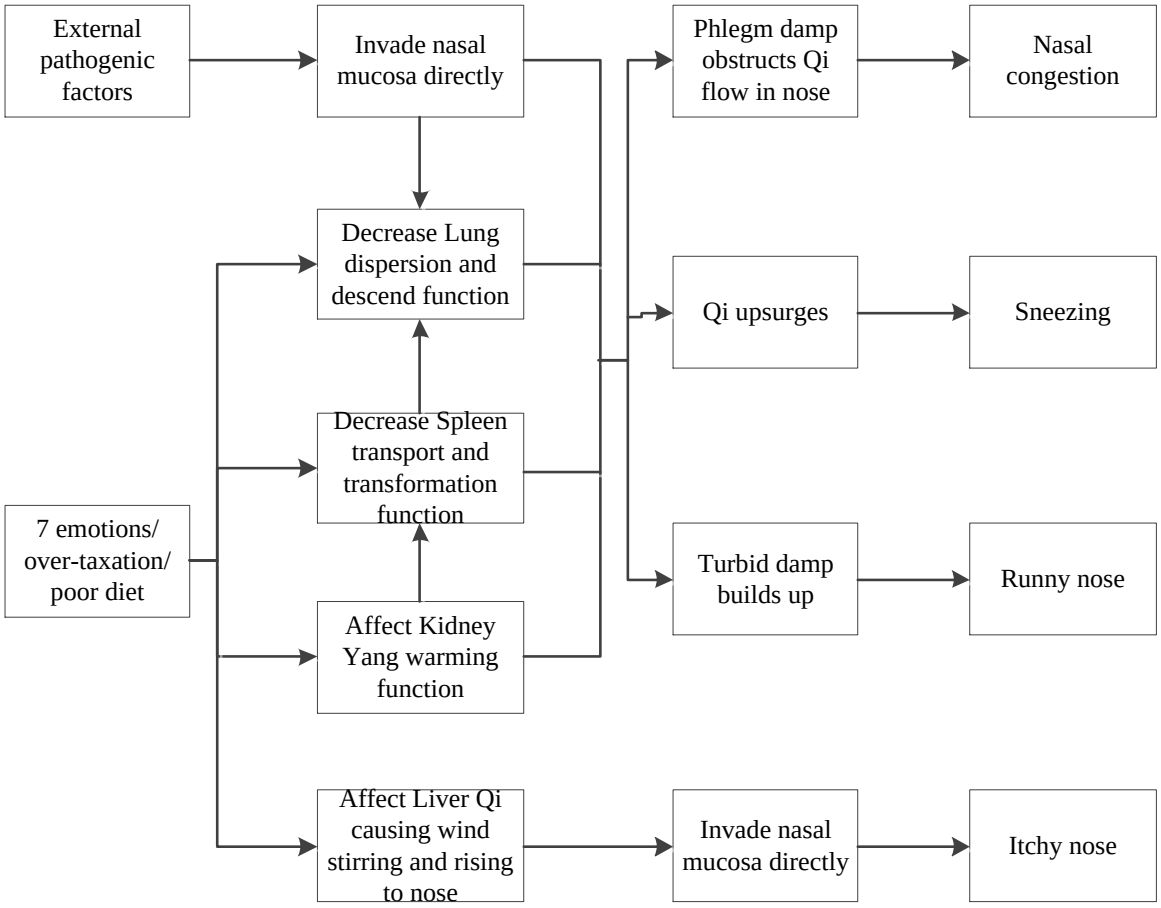


Figure 8. Aetiology and pathogenesis for AR in CM

3.5. Differentiation of syndromes of AR in CM

The differential diagnoses of AR in CM vastly differ from WM approach of disease differentiation. CM diagnosis is to determine a syndrome or a pattern of a group of signs and symptoms and based on connotative descriptions. Differentiation in CM is an individual centred and microcosmic approach, which may manifest in four main patterns (D. J. Xiong & Liu, 2013) as below:

3.5.1. Lung deficiency (cold damage) causing Wei Qi disharmony

Wei Qi (or defensive Qi) primarily lies in the interstitial spaces of the skin and the muscles, also known as the Cou Li. Anatomically, Cou Li refers to the epidermis and the dermis (Maciocia, 2008). In CM, Wei Qi dwells in the dermis and is regarded as the first barrier of

defence where it wards off pathogenic factors. Wei Qi is maintained in tandem with the Lung Qi. Weakness in the Lung Qi to diffuse the fluids, regulate sweating and control the pores can cause pathogenic factors to infiltrate the slack (cold invasion) or tight pores (lack of sweating may amount to increase of internal heat) (Maciocia, 2008). This imbalance signifies a lack of Lung Qi to maintain the defensive Qi in the Cou Li, which renders it susceptible to pathogenic factors especially Wind and Cold pathogens. Therefore, manifestations of itchiness, sneezing and blockage in nose can emerge.

3.5.2. Spleen Qi deficiency inhibiting clear Yang rising

The Spleen and the Lung in CM perspective are interrelated by the formation, nourishment and the movement of Qi. CM regards the Spleen as part of the digestive system. The Spleen primarily transforms and transports food essences and ascends clear Yang Qi to the Lung. The Lung regulates Qi by diffusing it and descending it to other organs. With the deficiency of Spleen Qi, the clear Yang rising is inhibited. When Lung Qi is affected with the inhibition of the clear Yang rising, its diffusion function is impaired (Maciocia, 2008). Water metabolism is also a part of the Spleen and Lung function. The Spleen separates the usable and the unusable parts of fluids ingested; the clear part goes upwards to the Lung to be distributed to the Cou Li, and the turbid part goes downwards to the intestines where it is eliminated through the bladder (Maciocia, 2008). If the Spleen Qi is impaired, this will affect the Lung diffusion, which in turn will generate dampness. With impaired Qi diffusion, the Lung is not able to fend off external pathogenic factor, and the nose will be runny.

3.5.3. Kidney Qi deficiency inhibiting dispersion of warm Yang Qi to orifices

The Lung is also responsible for the descending of the Qi and fluids to the Kidney, in turn the Kidney Yang evaporates the fluids and sends the clear mist up to the Lung to moisten the organs and the nasal orifices. Insufficient Kidney Qi can produce a lack of Kidney Yang, this can

compromise the ascending and the descending mechanism of Qi as well as the fluids between the Lung and the Kidney (Maciocia, 2008). With this impairment, susceptibility to cold attack of the Lung, fluid retention can cause an accumulation of nasal mucus often associated with nasal congestion and runny nose.

3.5.4. Heat attack at Lung meridian surging and assailing the nasal orifices

Heat attack at Lung meridian is a result of accumulated heat in the meridian causing the counter flow of Qi to assail the orifices (D. J. Xiong & Liu, 2013). Signs and symptoms of profuse sneezing and nasal congestion with thick yellow or green discharge often take place on humid hot days instead of cold days (D. J. Xiong & Liu, 2013).

3.6. Management of AR in CM

AR has been managed by various CM modalities including CHM, acupuncture, ear acupuncture / ear acupressure and Tui Na.

3.6.1. Chinese herbal medicine

CHM is an important modality in CM, utilising Chinese medicinal formulae (mixture of Chinese herbs according to CM theories) to treat ailments. The nomenclature "Chinese herbal medicine" encompasses nature-derived products from trees, leaves, roots and bark, minerals and animal materials. These natural products have contributed in one way or another to the development of drug discoveries. For treatment of AR, CHM usage is widespread and has existed since the advent of second millennia. Application of CHM for AR by clinicians is diverse in nature owing to the extent variety of herbs in CM. Unlike Western pharmacotherapy, standardisation of the herbal formulae used for AR treatment is an insurmountable endeavour owing to diversity associated with CHM usage in CM clinical practice. Based on the pattern differentiations of AR in CM, there are common herbs that are used to treat the different patterns

of AR based on CM treatment principles. The treatment principles with commonly used CHMs are summarised in Table 14 (D. J. Xiong & Liu, 2013).

Table 14. Treatment principles with common herbs used for different patterns of AR

Treatment principles for the different patterns of AR	**Common herbs used**
Tonify Lung Qi, strengthen Wei Qi and dispel cold	Ren Shen (*Ginseng et Rhizoma*)
	Gan Cao (*Glycyrrhizae et Rhizoma*)
	He Zi (*Chebulae Fructus*)
	Xi Xin (*Asari Radix et Rhizoma*)
	Jing Jie (*Schizonepetae Herba*)
	Jie Geng (*Platycondonis Radix*)
	Yu Nao Shi (*Asteriscus Pseudosciaenae*)
	Chan Tui (*Cicidae Periostracum*)
	Gan Jiang (*Zingiber*is *Rhizoma*)
Tonify Qi, strengthen Spleen and penetrate Yang	Ze Xie (*Alismatis Rhizoma*)
	Xin Yi Hua (*Magnoliae Flos*)
	Bai Zhu (*Atractylodis Macrocephalae Rhizoma*)
	Xi Xin (*Asari Radix et Rhizoma*)
	Shan Yao (*Dioscoreae Rhizoma*)
	Gan Jiang (*Zingiberis Rhizoma*)
	Sha Ren (*Amomi Fructus*)
	Fang Feng (*Saposhnikoviae Radix*)
	Gui Zhi (*Cinnamomi Ramulus*)
Warm Kidney Yang, strength Kidney Qi and regulate Qi	Rou Gui (*Cinnamomi Cortex*)
	Fu Zi (*Aconiti Lateralis Radix Preparata*)
	Ban Xia (*Pinelliae Rhizoma*)
	Chen Pi (*Citri Reticulatae Pericarpium*)
	Yi Yi Ren (*Coicis Semen*)
	Gan Jiang (*Zingiberis Rhizoma*)
	Ren Shen (*Ginseng et Rhizoma*)
	Wu Zhu Yu(*Euodiae Fructus*)
	Huang Qi (*Astragali Radix*)
	Fang Feng (*Saposhnikoviae Radix*)
Cool heat in the Lung and open nasal orifices	Huang Qi (*Astragali Radix*)
	Zhi Zi (*Gardeniae Fructus*
	Shi Gao (*Gypsum Fibrosum*)
	Zhi Mu (*Anemarrhenae Rhizoma*)
	Sang Bai Pi (*Mori Cortex*)
	Xin Yi Hua (*Magnoliae Flos*)
	Pi Pa Ye *(Eriobotryae Folium*)
	Bai He (*Lily Bulbus*)
	Mai Dong (*Ophiopogonis Radix*)

3.6.2. Acupuncture

Acupuncture is a technique of insertion and manipulation of fine needles in specific points on the human body. The therapeutic effects of acupuncture rely on the practitioner's knowledge of specific locations on anatomical landmarks for particular diseases to yield optimum outcome.

Clinical studies have shown that treatment of AR patients using acupuncture demonstrated significant relief of the symptoms (Brinkhaus et al., 2013; A. R. Kim et al., 2011).

A recent clinical practice guideline for management of AR published by American Academy of Otolaryngology – Head and Neck Surgery Foundation in the US has confirmed positive evaluation of acupuncture as a non-pharmacologic therapeutic option for patients (Seidman et al., 2015). The evidence quality aggregate attributed to acupuncture was rated grade B, based on the assessment of RCTs and observational studies with consistent effects. It endorsed acupuncture as an effective alternative to medical therapies that reduced AR-related symptoms and improved quality of life.

3.6.3. Ear acupuncture and ear acupressure

Similarly, the principle of ear acupuncture and ear acupressure lies in the basis that the human body microsystem is superimposed on the auricle, with specific points that correspond to different parts of the body. Ear acupuncture or ear acupressure is a method of stimulating the points by attaching dermal needle or pellets on the locations of the ear. To attach dermal needle or pellets on the specific locations of the ear for the treatment of ailments, a skilled practitioner is required. For ear acupressure, after the pellets are applied, the patients are able to self-administer the process by simply pressing on it and controlling the intensity of the pressure. A SR including five RCTs concluded that ear-acupressure seemed more effective than anti-histamines for long-term effects (C. S. Zhang et al., 2010).

3.6.4. Massage therapy (Tui Na)

Tui Na is a massage therapy in CM that is more than mere massage. Its therapeutic approach is targeted at invigorating the flow of Qi and blood, lubricating and relaxing the joints and expelling, clearing as well as dredging the pathogenic factors (Pritchard, 2010). It encompasses a gamut of techniques ranging from passive movements to active strike movements directed at the points, channels and collaterals in the body. Tui Na essentially embraces the principles of CM. A clinical study was conducted on 60 AR afflicted children, who were randomised into Tui Na group and Western medication (WM) group (Ye et al., 2016). The outcome after four weeks of treatment was that nasal symptoms associated with AR were significantly improved in both groups with Tui Na group being more remarkable in outcome. The effective rate of Tui Na was 90% versus 73.3% for WM (Loratadine).

3.7. Comments

The modalities CHM, acupuncture, ear acupuncture and ear acupressure as well as Tui Na stem from a long history of use in CM from China. Its popularity and demand by the populace has propelled research on their efficacies in each of these modalities. Discovery on the use of *artemisia annua* L. (Qing Hao), a common herb used in CM, containing artemisinin, is currently used as anti-malaria monoclonal therapy drug. This has prompted the scientific community to look for curatives in natural products for discovery of new drugs. In this respect, more CM modalities are cast into research framework of chronic diseases, where it is hoped that historic long-honoured use of traditional CM practice can provide an answer to maladies.

In recent years, RCTs and experimental studies on CHM formulae for the treatment of AR have researched intensively. The clinical practice guideline for AR (2015) cited limited knowledge of CHM products and a lack of access to Chinese literature on RCTs for AR contributed to a bias for its use by the panel members. Inadequate evidence, lack of access to literature and contradictory results of clinical studies pose a significant challenge for both clinicians as well as patients who are end users of CHMs.

Positive outcome of an 18-herb formulation (RCM-101) for treatment of SAR in a clinical trial showed moderate to marked rates (60.7%) of improvement for symptomatic relief of AR sufferers (C.C.L. Xue, Thien, Zhang, Da Costa, & Li, 2003). Matkovic et.al (2010) also revealed significant treatment efficacy of Huang Qi (*Astralgali Radix*) in a clinical trial of 48 adult patients with moderate to severe SAR. The outcome of this study depicted positive results in the symptom score, quality of life, specific IgE and IgG, nasal eosinophils, and physicians' and patients' global evaluation. Intensity of rhinorrhoea was decreased markedly. All indicators attested to therapeutic effects of the herb for SAR treatment. On the contrary, another RCT on

herbal preparation of an eight-herb formulation (RCM-102) did not find any significant difference between the active and placebo group for patients with SAR (Lenon et al., 2012).

Experimental studies have proven that CHM are effective in pharmacological actions. RCM-101 was discovered to inhibit proinflammatory mediators, inducible nitric oxide (Lenon, Li, Xue, Thien, & Story, 2008), histamine, leukotriene B_4 and PGE_2 in rat cultured cells (Lenon et al., 2007). Jung, Jung, Cheong, Kang, and Park (2012) also investigated the anti-allergic effect of a polyherbal formula of five herbs on ovalbumin-induced AR in mice manifesting marked reduction in the serum levels of histamine as well as OVA-specific IgE and TNF. Anti-inflammatory effects have also been detected with different CHM formulae traditionally used to treat AR. A new mixed formula consisting of Shin-yi-san, Xiao Qing Long Tang and Xiang Sha Liu Jun Zi Tang was discovered to have a beneficial effect on patients suffering from PAR (Yang, Hong, & Yu, 2002). Stimulatory effects on polymorphonuclear neutrophils (PMN) were attenuated and nasal discharge (not serum) from AR group with high serum IgE was abolished three months after treatment. A Taiwanese study indicated the use of Bu Zhong Yi Qi Tang suppressed the IgE, IL4-stimulated production of PGE_2 and LTC_4 by PMN in PAR patients (Yang & Yu, 2008). Overall, nasal symptom score was improved for the active group. However, this study also indicated another formula Ping Wei San was not effective for the treatment of PAR.

To date, although there exist many RCTs involving the different types of herbs and formulae used for the management of AR, no systematic review has been conducted on the entirety of RCTs on CHM for AR treatment. The existing RCTs are commonly questioned for small sample size and methodology. In recent years, RCTs and experimental studies on CHM formulae for the treatment of AR have researched intensively. The clinical practice guideline for AR cited limited knowledge of CHM products and a lack of access to Chinese language on

RCTs for AR contributed to a bias for its use by the panel members (Seidman et al. 2015). Inadequate evidence, lack of access to literature and contradictory results of clinical studies pose a significant challenge for both clinicians as well as patients who are end users of CHMs. The inclusion of acupuncture in the latest revision of evidence-based clinical practice guideline on AR in Seidman et al. (2015) has inspired research in other areas of CM. There is a need to conduct thorough reviews for AR in clinical and experimental studies to develop a comprehensive profile of CHM for AR.

Chapter 4 Methodologies

This chapter describes the methodologies employed in the SR of RCTs, the reviews of experimental studies and the classical data mining in relation to AR.

4.1. Methods of systematic review of RCTs

This SR was conducted adhering to the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 (Higgins & Green, 2011).

4.1.1. Search strategies

The search strategies and the initial literature search was developed and conducted with the support from the Cochrane Collaboration ENT group up to 2014. A second phase search was updated up to April 2016, of which the similar search strategies were adopted. The series of literature searches were conducted to identify suitable RCTs to be included in the review. There were no restrictions on the language; publication year; or publication status imposed on this SR. There are three *modus operandi* in the approaches of searches:

i. Electronic searches

Twenty electronic databases were searched from their inceptions for published; unpublished; and ongoing trials. They include the Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library* Issue 4, 2016); PubMed; EMBASE; China National Knowledge Infrastructure (CNKI); Chong Qing VIP (CQVIP); Wanfang Data; AMED; CINAHL; LILACS; KoreaMed; IndMed; PakMediNet; CAB Abstracts; Web of Science; BIOSIS Previews; ISCTRN; ClinicalTrials.gov; ICTRP; and Google. All search strategies for the databases were based on the search design for CENTRAL. Adaptations of the highly sensitive search strategy designed by the Cochrane Collaboration for identifying RCTs and controlled clinical trials (as described in *The Cochrane*

Handbook for Systematic Reviews of Interventions Version 5.1.0 (Higgins & Green, 2011) were combined with subject strategies, where appropriate.

Keywords used for the literature search included the following: allergic rhinitis, rhinitis, pollionosis, Chinese herbal medicine, herbal medicine, phytomedicine, ethnobotanical, pharmacognosy and their synonyms.

ii. Searching other resources

In addition, the reference lists of identified publications for RCTs were scanned. Further search was conducted on PubMed, TRIP database, The Cochrane Library and Google to retrieve existing systematic reviews relevant to this systematic review, so that reference lists for additional trials could be scanned. Using the Cochrane Ear, Nose and Throat Disorders Group Trials Register, the conference abstracts were also part of the reference lists.

iii. Hand search

The following journals published in Chinese were hand searched: the Chinese Journal of Otorhinolaryngology of Integrated Traditional and Western Medicine (1993 onwards), the Chinese Journal of the Practical Chinese with Modern Medicine (1988 onwards), and the Chinese Journal of Integrated Traditional and Western Medicine (1981 onwards). Proceedings of the World Congress of Chinese Medicine held in 2003, 2006, 2008, 2009 and 2011 were included within the hand search.

4.1.2. Selection criteria

The selection criteria for the RCTs involved four broad variables, which included types of studies, types of participants, types of interventions and types of outcome measures.

i. Types of studies

RCTs and quasi-randomised trials, with or without blinding, regardless of language and publication type were considered. If randomised cross-over trials were included, only data from the first phase were used for data analysis.

ii. Types of participants

Patients, male or female, of any age, with SAR or PAR were included. Allergy must be proven using an objective test such as a skin prick test or a specific IgE test (eg. RAST).

iii. Types of interventions

Any form (e.g. decoction, capsule, tablet, pill or powder) of single herb or Chinese medicinal formulae compared with the following control interventions: placebo, no intervention or conventional therapies, irrespective of methods of administration or dosage were considered as a form of intervention. CHM combined with other treatments, such as acupuncture, was also included. Co-interventions were allowed as long as all trial arms received the same co-intervention.

iv. Types of outcome measures

The outcome measures encompassed both primary and secondary for systematic evaluation. These are the followings:

Primary outcomes

- Improvement of symptoms including nasal symptoms (nasal congestion, rhinorrhoea, sneezing, itchy nose) and non-nasal symptoms (itchy eyes, watery eyes and itchy ears), using symptom scores or scales.

Secondary outcomes

- Quality of life (e.g. RQLQ, SF-36, defined by trial reports)
- Medication consumption (scores)
- Serum IgE level
- Adverse events

Independent selection of studies according to the inclusion criteria was carried out by two reviewers (JK and AY). Any discrepancy between the two reviewers was resolved by discussion or consulted with third party. Plans were arranged to contact the authors of original studies to clarify any unclear issues or to obtain any additional data when needed. However, after ten unresponsive contacts through emails, we decided to assess the studies based on published data only.

4.1.3. Data extraction

Data were extracted based on a self-developed data extraction form. If papers in a language other than English and Chinese were identified, their data were extracted with translation in English with the help of other researchers. The data to be extracted from each included trial consisted of study characteristics such as: study setting, sample size, risk of bias, inclusion criteria, diagnostic criteria, and characteristics of participants, interventions and outcome measures. If the data on the number of patients with each outcome measured were not available in the paper, further information was sought by contacting the chief investigator. However, owing to no response from initial contacts, analysis was carried out on reported data only.

4.1.4. Data analysis

i. Assessment of risk of bias in included studies

The risk of bias in the studies was assessed independently by JK and AY. Any inconsistency between the two authors was resolved by discussion. The following risk of bias assessment domains and the considerations were based on the Cochrane Handbook for Systematic Reviews of Interventions 5.1.0 (Higgins & Green, 2011):

- Random sequence generation (selection bias) – Was there a randomised method adopted by the investigators? If so, what was the method?
- Allocation concealment (selection bias) – Was the allocation adequately concealed? Could the investigators foresee means where selection bias could be introduced in the allocation procedures?
- Blinding of participants, personnel and outcome assessors (performance bias) – Was the knowledge of the allocated interventions adequately prevented during the study known as blinding?
- Blinding of outcome assessment – Were the study and outcome measurement blinded?
- Incomplete outcome data (attrition bias) – Was there an imbalance of numbers or reasons for missing data reported in the intervention group? For reporting dichotomous data, was the proportion of the missing outcomes compared with observed event risk likely to create clinical relevant bias in an estimate? For reporting continuous outcome data, was the effect size among the missing data outcomes likely to induce clinically relevant bias in observed effect?
- Selective outcome reporting (reporting bias) – Were the reports of the study free of suggestion of selective outcome reporting? Was the study protocol readily available with the criteria pre-specified with primary and secondary outcomes?

- Other bias – Was the study free from other problems associated with specific study design used, any extreme baseline imbalance or external funding?

For heterogeneity assessment, I^2 statistics was used. According to the Cochrane handbook (Higgins & Green, 2011), I2 between 0% and 30% was considered low. 30% to 50% as moderate and 50% to 100% as substantial. The overall synthesis was performed qualitatively or quantitatively according to categorical, continuous and risk of bias analyses of the trials. For outcome measures, both dichotomous data and continuous data were utilised in the SR. Dichotomous data refer to where the effect measures are presented as a binary form for the relative risk (RR) which is the ratio of risk for an event in the intervention groups (Higgins & Green, 2011). Meta-analysis for continuous data was applied to studies where all reported on the outcome measure: the same scale for mean difference (MD); different scale for standardised mean difference (SMD) (Higgins & Green, 2011). Dichotomous data as RR and continuous data as MD or SMD, both with 95% confidence intervals (CI) using inverse variance with random-effects methods were presented. An intention-to-treat (ITT) analysis was performed where possible. A "worst-case scenario" method was used as a solution to address the missing data. Synthesis of the data were conducted on the Cochrane software RevMan 5.3 (The Cochrane Collaborations, 2014).

ii. Frequency of commonly used herbs

In the process of the SR, the frequency of the most commonly used herbs in the included RCTs was also extracted. This was conducted after the included studies were finalised where characteristics of each studies were extracted and downloaded on pre–formatted Excel layout. The formulae of the herbs used and the number of herbs identified in the studies reported were collated. From the synthesis, the ranking and the frequency usage of top 10 herbs used in the RCTs were extracted.

4.2. Methods of review for CHM in experimental studies

Based on the outcome of the SR, an evaluation was conducted on the five most frequently used in the RCTs. The objective was to review possible chemical compounds that elicit mechanisms of actions of these most commonly used herbs in their effects on AR and other diseases.

4.2.1. Search strategies

Searches were conducted on the following databases: PubMed, The Cochrane Library (Database of Abstracts of Reviews of Effects, DARE, issue 4 April 2015); EMBASE(Ovid); ProQuest; AMED; MEDLINE; CINAHL; ScienceDirect; SCOPUS; Web of Science; CNKI; CQVIP and Wanfang data. The search included English and Chinese terminologies such as AR [Guo Min Xing Bi Yan, 过敏性鼻炎], CHM [Zhong Yao, 中药], animal studies [Dong Wu Yan Jiu, 动物研究], Fang Feng (*Saposhnikoviae Radix*), Huang Qi (*Astragalus Radix*), Xin Yi (*Magnoliae Flos*), Cang Er Zi (*Xanthii Fructus*), Xi Xin (*Asari Radix et Rhizoma*) and their synonyms.

4.2.2. Data extraction and analysis

Relevant experimental studies (both animal experiments and natural products analyses) were extracted and downloaded onto reference management software. The studies are grouped accordingly under different herbs, then sorted under the clinical mechanism of actions. Following, these herbs were further subgrouped according to their bioactive chemical compounds and pharmacological actions.

4.3. Methods of review for CHM in classic literature

4.3.1. Search strategies

Two sets of classical texts were used namely, Encyclopaedia of Traditional Chinese Medicine (Zhong Hua Yi Dian) (ZHYD) (R. Hu, 2015) and The Complete Collection of Traditional Texts on Chinese Materia Medica (Zhong Guo Ben Cao Quan Shu) (ZGBCQS) (Lu, 1999). The classical texts are mainly made up of connotative descriptions of symptoms and prescriptions of herbs for myriad of maladies. Electronic search was conducted on the ZHYD which consists of 1,156 books while ZGBCQS containing 740 books (2,027 titles), a hand search was performed.

Keywords used were associated with AR-like symptoms. The keyword search commenced with the word 鼻 (nose) in both texts. Subsequent keywords included 喷嚏 (sneeze), 鼻塞浊涕 (congested nose with turbid nose discharge), 鼻塞流清涕 (congested nose with clear runny nose discharge), 鼻壅 (nasal obstruction), 鼻塞不通/鼻塞 or 鼻塞不通利 (nasal congestion), 鼻鼽 (allergic rhinitis) and 鼻痒 (itchy nose). Descriptions of comorbid conditions are often accompanied with the foregoing main keywords. These comorbid descriptions 精神昏闷 (listlessness), 精神不爽 (general unwellness), 头目疼痛 (headache, eye pain), 鼻痛 (pain in the nose) and 鼻准赤色 (red nose) were employed in the search.

4.3.2. Selection criteria

The selection criteria for ZHYD and ZBGCQS were based on one keyword to filter the data and set aside words relating to nasal pathologies. Therefore, the word 鼻 (nose) was used from the onset. Downloaded articles were then sorted with the keyword relating to AR-like keywords. Words that are not related to the AR nasal descriptions such as 鼻生瘕肉谓之鼈 (nasal polyps),

and 鼻渊 /鼻渊不止 (sinusitis) were excluded. Similarly, for acupuncture treatments for AR and diagnosis descriptions without herbal intervention records were also excluded. Other nasal pathologies that were not associated with AR-like conditions were excluded automatically.

4.3.3. Data extraction and analysis

i. Data mining process

The articles of ZHYD and ZGBCQS consist of citations of herbs used to treat AR-like signs and symptoms. These citations are essentially representations of clinical instances recorded by the author-clinicians. Data of ZHYD were accessed electronically, while for the ZGBCQS, a hand search was carried. For ZGBCQS, photographic profiles were developed for articles and pages identified with descriptions of AR-like symptoms in the literature. These profiles were then downloaded onto computer program for screening and sorting. Two-step processes were undertaken henceforward. First, the raw data were input onto Excel for both ZHYD and ZGBCQS. The data were sorted and combined. Then the data were transferred and transposed onto analytic software, Statistical Package for the Social Sciences (SPSS) version 23 for data analysis (IBM Corp, 2015). The combined data were evaluated for frequency of citations for the types of herbs used in AR-like conditions as well as the ranking of the herbs.

ii. Principal component analysis and hierarchical cluster analysis

Aside from the frequency, syndromic categorisation was conducted to identify the variety of herbs used to target specific AR-like signs and symptoms in the literature by means of PCA and HCA. SPSS is the software platform that was used to perform both multivariate statistical methods for pattern associations in the herbs prescribed for AR-like sign and symptoms and their characteristics according to the keywords searched in the search strategies. PCA was used to determine the variable dimension and it emphasises on the variation and elicit strong patterns in a large dataset by replicating total variance among large sets of variables (Rencher &

Christensen, 2012). Correlations or "loadings" are calculated based on the weighted average of the eigenvalues. Loadings are the determinants of the variable's positon within the circle of correlation while eigenvalues are indicators of the variance of a component (Abi& Williams 2010). Eigenvalues that are similar in magnitude indicate comparable variability in components' dimensions (Raykov & Marcoulides, 2012). The importance of a component is determined based on the sum of squared coefficients of correlations between a variable (herb) and all components when eigenvalue is equal to or more than 1 (Abi & Williams 2010). When eigenvalue is less than the value of 1, the component is of less importance. HCA is an exploratory statistical method which charts the distance matrix of these herbs and groups these herbs into meaningful datasets by using squared Euclidean distance. The squared Euclidean distance was calculated by means of using average linking between groups method on the SPSS. Clustering creates and merges similar groupings of herbs with similar characteristics in a predetermined format. These visual analyses could offer a meaningful interpretation as to the relevance and its relational aspects to each herb or to the AR-like signs and symptoms.

Chapter 5 Results I – SR of RCTs for the treatment of AR

This chapter reports the results of the SR that includes 62 RCTs according to the methods described in 4.1.

5.1. Selection of studies

A total of 4,342 records were identified and 62 RCTs were included in the reviews. The study selection process is illustrated in Figure 9 while the list of 62 included studies are summarised in Table 15. Study I.D. is assigned to each included study for the purpose of identification in this chapter.

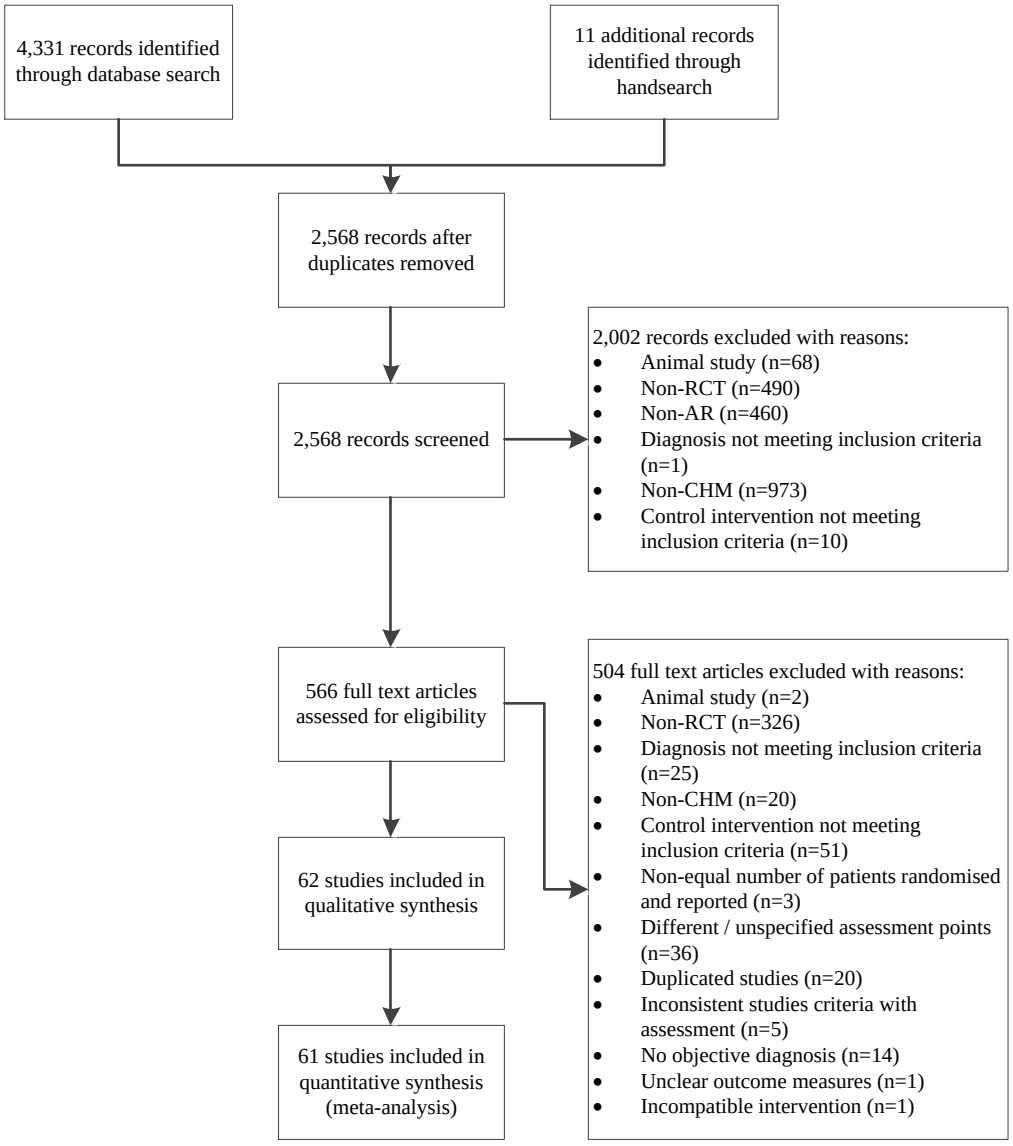


Figure 9. Study selection process for the included studies in the SR

Table 15. List of 62 included RCTs in SR

No.	Study I.D.	Included RCTs
1.	Baba 1995	Baba, S., & Takasaka, T. (1995). Double-blind clinical trial of Sho-seiryu-to (TJ-19) for perennial nasal allergy. *Clinical Otolaryngology*, 88(3), 389-405.
2.	Bao 2013	Bao, A. C., Zhu, J. J., & Gong, Q. (2013). Clinical observation of Xiaoqinglong mixture in the treatment of allergic rhinitis [Xiaoqinglongtang heji zhiliao bianyingxing biyan de linchuang guancha]. *China Modern Medicine*, 20(31), 109-110.
3.	Cao 2007	Cao, J. G., Ding, Y., & Cheng C.K. (2007). Clinical observation of Cang'erzi keli for the treatment of 30 cases with allergic rhinitis [Cang'erzi keli zhiliao bianyingxing biyan 30 li linchuang guancha]. *Xinan Junyi [Journal of Military Surgeon in Southwest China]*, 9(3), 71-72.
4.	Cao 2014b	Cao, Z. H., & Huang, F. Q. (2014). Xiangju joint capsule combined with claritin syrup treatment for 30 children with allergic rhinitis [Xiangju jiaonang lianhe kairuitan tangjiang zhiliao xiao'er guominxing biyan 30 li]. *Inner Mongolia Journal of Chinese Medicine [Neimenggu Zhongyiyao*], 2, 19-20.
5.	Chen 2012	Chen, J. J. (2012). *Effect of Chinese traditional medicine xingbi wenmin ningjiaoji in children with allergic rhinitis [Zhongyi xingbi wenmin ningjiaoji zhiliao xiao'er guominxing biyan de laixiao guancha]*. (Masters), Fujian University of Traditional Chinese Medicine, Fujian, China.
6.	Chen 2004	Chen, K., Luo H. X., Li, D. X., & Ye, B. X. (2004). The therapeutic effects of a combined therapy with radiofrequency thermocoagulation to the ethmoidal nerve under endoscope and Yupingfeng granule orally taking on perennial allergic rhinitis [Bineijingxia shepin rening shaiqian shenjing jiehe yupingfeng keli zhiliao changnianxing bianyingxing biyan]. *Chinese Journal of Otorhinolaryngology of Integrated Traditional and Western Medicine] [Zhongguo Zhongxiyi Jiehe Erbiyanhouke Zazhi]*, 12(4), 193-194.
7.	Chen 2014	Chen, L., & Chen, X. W. (2014). Analysis on therapeutic effect of Cetrizine combined with Yupingfengsan in treating allergic rhinitis [Xitiliqin lianhe Yupingfengsan zhiliao guominxing biyan liaoxiao fenxi]. *World Chinese Medicine*, 9(7), 880-882.
8.	Chen 2011	Chen, Y. T., & Chen, G. Q. (2011). Jiawei Yupingfengsan with budesonide nasal spray in the treatment of 46 allergic rhinitis cases [Jiawei Yupingfengsan peihe budinaide bipenwuji zhiliao bianyingxing biyan 46 li]. *Shaanxi Journal of Traditional Chinese Medicine [Shaanxi Zhongyi]*, 32(7).
9.	Gao 2009	Gao, Y. (2009). *The effect of Poria, Cinnamon Twig, Ovate Atractylodes, and Liarice decoction on quality of life of patients with perennial allergic rhinitis [Lingguizhugantang jiawei zhiliao changnianxing bianyingxing biyan de liaoxiao guancha ji dui huanzhe shenghuo zhiliang de yingxiang]*. (Masters), Chengdu University of Traditional Chinese Medicine [Chengdu Zhongyiyao Daxue], Chengdu, China.
10.	Guo 2010	Guo, J. F., Zhao, Z., & Kong, Q. (2010). Clinical effects of allergic rhinitis with Qufeng zhiyang koufuye [Qufeng zhiyang koufuye zhiliao guominxing biyan liaoxiao guancha]. *Hubei Journal of Traditional Chinese Medicine [Hubei Zhongyi Zazhi]*, 32(10), 24-25.
11.	Han 2002	Han H. Y., & Wang, D. H. (2002). Long term effects of kidney tonifying and warming lung capsule for the treatment of allergic rhinitis [Bushenwenfei jiaonang zhiliao guominxing biyan de yuanqi liaoxiao guancha]. *Chinese Journal of Otorhinolaryngology of Integrated Traditional and Western Medicine [Zhongguo Zhongxiyi Jiehe Erbiyanhouke Zazhi*], 10(5), 233-234.

No.	Study I.D.	Included RCTs
12.	Hong 2005	Hong, W., Liu, A. H., Hong, Y., & Fang, Z. W. (2005). Clinical study of compounds for allergic rhinitis [Fufang biyantang zhiliao bianyingxing biyan de linchuang yanjiu]. *Practical Clinical Journal of Integrated Traditional Chinese and Western Medicine [Shiyong Zhongxiyi Jiehe Linchuang]*, 5(5), 41-42.
13.	Hu 2002	Hu, G., Walls, R. S., Bass, D., Ramon, B., Grayson, D., Jones, M., & Gebski, V. (2002). The Chinese herbal formulation Biminne in management of perennial allergic rhinitis: a randomized, double-blind, placebo-controlled, 12-week clinical trial. *Annals of Allergy, Asthma & Immunology*, 88(5), 478-487.
14.	Huang 2008a	Huang, G. F. (2008). Impact of Wenfeizhiliu pills for perennial allergic rhinitis sufferers in peripheral blood IL4 and IFN-r [Wenfeizhiliudan dui changnianxing bianyingxing biyan huanzhe xueqing IL-4, IFN-r de yingxiang]. *Jilin Journal of Traditional Chinese Medicine [Jilin Zhongyi Yao]*, 28(12), 884-885.
15.	Huang 2010	Huang, P., Yu, Y. B., & Ma, Z. X. (2010). Clinical study on "Jiemin Qufeng Decoction II" in treating allergic rhinitis [Jiemin qufeng erhaofang zhiliao bianyingxing biyan linchuang yanjiu]. *Shanghai Journal of Traditional Chinese Medicine [Shanghai Zhongyiyao* Zazhi], 44(3), 32-34.
16.	Huang 2006b	Huang, Z. Y. (2006). Bimin nasal irrigation for the treatment of 71 cases of allergic rhinitis [Biminshui zhiliao biantai fanyingxing biyan 71 li]. *Guangxi Journal of Traditional Chinese Medicine [Guangxi Zhongyi Yao]*, 29(2), 21-22.
17.	Jiang 1997	Jiang, Z. J. (1997). Clinical effects of Yufengjianbitang in perennial allergic rhinitis [Yufengjianbitang zhiliao changnianxing bianyingxing biyan liaoxiao guancha. *Chinese Journal of Primary Medicine [Zhongguo Ji Ceng Yixue]*, 4(4), 36-37.
18.	Jin 2010	Jin, H. M. (2010). Clinical observation of Kemin decoction in treating perennial allergic rhinitis [Kemintang zhiliao changnianxing bianyingxing biyan linchuang guancha]. *Chinese Journal of Traditional Chinese Medicine and Pharmacy [Zhonghua Zhongyiyao Zazhi]*, 25(12), 2192-2193.
19.	Jung 2011	Jung, J. W., Kang, H. R., Ji, G. E., Park, M. S., Song, W. J., Kim, M. H., . . . Min, K. U. (2011). Therapeutic effects of fermented red ginseng in allergic rhinitis: A randomized, double-blind, placebo-controlled study. *Allergy, Asthma & Immunology Research*, 3(2), 103-110.
20.	Lenon 2012	Lenon, G. B., Li, C. G., Da Costa, C., Thien, F. C. K., Shen, Y., & Xue, C. C. L. (2012). Lack of efficacy of a herbal preparation (RCM-102) for seasonal allergic rhinitis: A double blind, randomised, placebo-controlled trial. *Asia Pacific Allergy*, 2(3), 187-194.
21.	Li 2012c	Li, Q. L. (2012). Differential treatment of 52 cases of allergic rhinitis [Bianzheng zhiliao guominxing biyan 52 li liaoxiao guancha]. *Zhejiang Chinese Medicine Journal [Zhejiang Zhongyi Zhazhi]*, 47(10), 717-718.
22.	Li 2012b	Li, R. (2012). Integrated Chinese medicine and Western medicine for the treatment of 80 cases of children with allergic rhinitis [Zhongxiyao jiehe zhiliao ertong guominxing biyan 80 li liaoxiao guancha]. *Chinese Journal of Clinical Rational Drug Use [Linchuang Heli Yongyao]*, 5(4), 69.
23.	Li 2008	Li, S. L. (2008). Clinical efficacy of combined Chinese medicine and Western medicine for 30 cases of allergic rhinitis [Zhongxiyi jiehe zhiliao bianyingxing biyan 30 li linchuang guancha]. *Guiding Journal of TCM [Zhongyi Zhidao Bao]*, 3, 50-53.

No.	Study I.D.	Included RCTs
24.	Liang 2011	Liang, S. Q. (2011). Clinical observation of modified Spleen qi deficiency Buzhongyiqitang for the treatment of perennial allergic rhinitis [Jiawei buzhongyizitang zhiliao feiqiquxing changnianxing bianyingxing biyan de linchuang zhiliao guancha]. *China Health Industry [Zhongyi Weisheng Chanye]*, 8(5), 100-101.
25.	Lin 2013	Lin, S. (2013). Clinical observation on 60 cases of children with allergic rhinitis treated by integrative medicine [Zhongxiyi jiehe zhiliao xiaoer guominxing biyan 60 li linchuang guancha]. *Fujian Journal of Traditional Chinese Medicine*, 44(2), 14-15.
26.	Liu 2004b	Liu, G., & Song, R. H. (2004). A clinical observation on the therapeutic effects of a combined therapy with dibiling nose dropping and septum rectifying operation on allergic rhinitis [Dibiling peihe shoushu jiaozheng bizhongge pianqu zhiliao bianyingxing biyan de linchuang guancha]. *Chinese Journal of Otorhinolaryngology of Integrated Traditional and Western Medicine [Zhongguo Zhongxiyi Jiehe Erbiyanhouke Zazhi]*, 12(1), 20-21.
27.	Liu 2001	Liu, Q. P., Liu, J. H., Li, Y. L., & Ge, Y. H. (2001). Nourishing Liver Yin in the treatment of allergic rhinitis [Yangyin pingganfa zhiliao biantai fanyingxing biyan]. *Journal of Beijing University of Traditional Chinese Medicine [Beijing Zhongyiyao Daxue Xuebao*], 24(2), 68-69.
28.	Lu 2011	Lu, B., Chang, K., Wang, H. J., Guo, J. J., & Chen, J. (2011). Regulating Ying and Wei in the treatment of 60 allergic rhinitis cases [Tiaohe yingweifa zhiliao guominxing biyan 60 li liaoxiao guancha]. *Shanxi Journal of Traditional Chinese Medicine [Shanxi Zhongyi]*, 27(3), 10-11.
29.	Lu 2003	Lu, B. Q., Sun, Y. F., Guo, Y. L., Xu, Q. W., & Zhou, X. J. (2003). A clinical observation on the therapeutic effects of a combined therapy with nasonex and bimin formula on allergic rhinitis [Neishuna bipenwuji lianhe zhongyao biminfang zhiliao bianyingxing biyan de linchuang guancha]. *Chinese Journal of Otorhinolaryngology of Integrated Traditional and Western Medicine [Zhongguo Zhongxiyi Jiehe Erbiyanhouke Zazhi]*, 11(6), 272-274.
30.	Lu 2009	Lu, J. (2009). Observation of Chinese and Western medicine for the treatment of 30 cases of perennial allergic rhinitis [Zhongxiyao heyong changnianxing bianyingxing biyan 30 li guancha]. *Journal of Practical Traditional Chinese Medicine [Shiyong Zhongyiyao Zazhi]*, 25(6), 380-381.
31.	Lu 1998	Lu, P., Shi, Y. M., & Xu, L. G. (1998). Integrative medicine clinical study of children with allergic rhinitis [Zhongxiyi jiehe zhiliao xiao'er guominxing biyan linchuang yanjiu]. Chinese *Journal of Integrated Traditional and Western Medicine [Zhongguo Zhongxiyi Jiehe Zazhi]*, 18(7), 437.
32.	Luo 2013	Luo, G. W. (2013). Qingretongqiaotang self-limiting treatment of pediatric wind-heat type of allergic rhinitis [Zini Qingretongqiaosan zhiliao xiaoer feijing fengrexing guominxing biyan]. *Journal of Emergency in Traditional Chinese Medicine [Zhongguo Zhongyi Jizhen]*, 22(12), 2095-2096.
33.	Matkovic 2010	Matkovic, Z., Zivkovic, V., Korica, M., Plavec, D., Pecanic, S., & Tudoric, N. (2010). Efficacy and safety of Astragalus membranaceus in the treatment of patients with seasonal allergic rhinitis. *Phytotherapy Research*, 24(2), 175-181.
34.	Peng 2001	Peng, S. L., Zhong, Q., & Huang, Q. S. (2001). Clinical observation of Biminling treatment in 36 allergic rhinitis cases [Biminling zhiliao bianyingxing biyan 36 li linchuang guancha]. *Chinese Journal of Information on Traditional Chinese Medicine [Zhongguo Zhongyiyao Xinxi Zazhi]*, 8(3), 58-59.

No.	Study I.D.	Included RCTs
35.	Peng 2004	Peng, S. L., Zhong, Q., & Yuan, X. H. (2004). Clinical observation on 42 cases of perennial allergic rhinitis treated by Sheti Zhiqiu granules [Shetizhiqiu keli zhiliao changnianxing bianyingxing biyan 42 li linchuang guancha]. *Journal of Traditional Chinese Medicine [Zhongyi Zazhi]*, 45(11), 836-837.
36.	Qin 2006	Qin, H. (2006). *The study of the clinical curative effect of the traditional Chinese medicine Biyanyihao granule for infusion in the treatment of PAR [Zhongyao biyan yihao chongji zhiliao changnianxing bianyingxing biyan de linchuang yanjiu]*. (Masters), Heilongjiang University of Traditional Chinese Medicine [Heilongjiang Zhongyiyao Daxue], Heilongjiang, China.
37.	Qiu 2012	Qiu, W. Y. (2012). *The allergic rhinitis TCM dialectical law and clinical research of Xiaoqinglong decoction treatment*. (Masters), Guangzhou University of Chinese medicine, Guangzhou, China.
38.	Shen 2004	Shen, F., & Chen, X. N. (2004). Xiaofeng granule treatment of allergic rhinitis in 80 cases [Xiaofeng chongji zhiliao bianyingxing biyan 80 li*]*. *Liaoning Journal of Traditional Chinese Medicine [Liaoning Zhongyi Zazhi]*, 31(1), 54.
39.	Shi 2014	Shi, H. Y., Zhuang, Y., & Wang, X. Y. (2014). Effect of Yupingfeng dropill in treatment of allergic rhinitis. Chinese Journal of Chinese *Materia Medica*, 29(22), 105-106.
40.	Shi 2012	Shi, Q. Y., & Zhao, Y. (2012). The therapeutic effect of Xiangju capsule of perennial allergic rhinitis observation [Xiangju jiaonang zhiliao changnian guominxing biyan de liaoxiao guancha]. *Medical Innovation of China [Zhongguo yixue chuangxing]*, 9(22), 105-106.
41.	Sun 2014a	Sun, R. H. (2014). Clinical observation of treatment of Tongqiao biyan capsules in allergic rhinitis [Tongqiao biyan jiaonang zhiliao guominxing biyan de linchuang guancha]. *Guangming Traditional Chinese Medicine [Guangming Zhongyi]*, 29(12), 2578-2588.
42.	Tang 2008	Tang, Y. Y., Song, K., Zeng. K.S., & Yang, M. F. (2008). Clinical observation on the therapeutic effects of supplemented four gentlemen decoction on perennial allergic rhinitis in the pattern of Spleen-Qi deficiency [Jiawei sijunzitang zhiliao piqixuxing changnianxing bianyingxing biyan de linchuang liaoxiao yanjiu]. *Chinese Journal of Otorhinolaryngology of Integrated Traditional and Western Medicine [Zhongguo Zhongxiyi Jiehe Erbiyanhouke Zazhi]*, 16(6), 422-424.
43.	Wang 2000a	Wang, D. H., Tang, H. Q., Ling, Y. X., Fu, X., Han, H. Y., & Li, Y. Z. (2000). Observation of recent desensitized nose drops to treat allergic rhinitis [Tuimin dibiye zhiliao guominxing biyan de jinqi liaoxiao guancha]. *Journal of Hunan College of TCM [Hunan Zhongyi Xueyuan Xuebao]*, 20(1), 43-45.
44.	Wu 2012a	Wu, J. P., Wan, Y., Xie, Z. S., & Cao, S., H. (2012). The clinical effects of Loratadine tablets with Xinqin Keli on treating allergic rhinitis [Qileitatin quhe xinqin keli zhiliao guominxing biyan de liaoxiao]. *Seek Medical and Ask The Medicine [Qiuyi wenyao]*, 10(10), 379.
45.	Wu 2009	Wu, M., Zhang, J. Y., Zhang, X., Ni, J. X., Lu, W. W., Ding, L. F., & Li, Z. (2009). Clinical observation of *Flos magnoliae* volatile oil nano-liposome nasal drops in treating pediatric allergic rhinitis [Xinyi huifayou nami zhizhiti dibiji zhiliao ertong bianyingxing biyan de linchuang guancha]. *Chinese Journal of Integrated Traditional and Western Medicine [Zhongguo Zhongxiyi Jiehe Zazhi]*, 29(8), 740-742.

No.	Study I.D.	Included RCTs
46.	Xiao 2015	Xiao, L., & Rao, X. H. (2015). Clinical efficacy of acupuncture combined with treatment of Chinese herb for allergic rhinitis [Zhenyao jiehe zihiliao guomin biyan de linchuang guancha]. *Journal of Zhejiang Chinese Medical University [Zhejiang Zhongyiyao Daxue Xuebao]*, 29(10), 762-763.
47.	Xie 2009	Xie, W., & Zhang, H. Z. (2009). Chinese herbs combined with radiofrequency treatment of allergic rhinitis analysis [Zhongyao lianhe denglizi shepin zhiliao bianyingxing biyan liaoxiao fenxi]. *Shandong Medical Journal [Shandong Yi Yao]*, 49(48), 66-77.
48.	Xin 2005	Xin, Y. J., & Li, C. F. (2005). A clinical observation on the therapeutic effects of treating method with Qi-boosting, Yang-warming and blood-quickening on perennial allergic rhinitis [Yiqiwenyanghuoxuefa zhiliao changnianxing bianyingxing biyan de liaoxiao guancha]. *Chinese Journal of Otorhinolaryngology of Integrated Traditional and Western Medicine [Zhongguo Zhongxiyi Jiehe Erbiyanhouke Zazhi]*, 13(2), 76-78.
49.	Xue 2003a	Xue, C. C., Thien, F. C., Zhang, J. J., Da Costa, C., & Li, C. G. (2003). Treatment for seasonal allergic rhinitis by Chinese herbal medicine: A randomized placebo controlled trial. *Alternative Therapies in Health and Medicine*, 9(5), 80-87.
50.	Xue 2003b	Xue, C. C., Thien, F. C., Zhang, J. J., Yang, W., Da Costa, C., & Li, C. G. (2003). Effect of adding a Chinese herbal preparation to acupuncture for seasonal allergic rhinitis: Randomised double-blind controlled trial. *Hong Kong Medical Journal*, 9(6), 427-434.
51.	Yan 2011	Yan, X. L. (2011). Allergic rhinitis treated with modified Yupingfengsan in 115 cases [Yupingfengsan jiawei zhiliao bianyingxing biyan 115 li linchuang guancha]. *Journal of Beijing University of Traditional Chinese Medicine [Beijing Zhongyiyao Daxue Xuebao]*, 34(5), 358-360.
52.	Yang 2004	Yang, Z. C. (2004). Observation on the effect of particle therapy of Xinqin in allergic rhinitis [Zhongyao xinqin keli zhiliao bianyingxing biyan liaoxiao guancha] Paper presented at the *Chinese Medical Association Eleventh National Symposium on Traditional Chinese Medicine ENT [Zhonghua Zhongyiyao Xuehui Quanguo Dishiyijie Zhongyi Erbihouke Xueshuyan Taohui]*, Chengdu, China.
53.	Ye 2015	Ye, J. L., & Lin, J. Z. (2015). Guizhitang combined with mahuangfuzixixin decoction for treatment of 32 cases of allergic rhinitis [Xixin tang jiajian zhiliao guominxing biyan 32 li]. *Fujian Journal of Traditional Chinese Medicine*, 46(2), 46-47.
54.	Zhang 1996	Zhang, H. Z., Ren, S. X., Tang, Y. H., Wang, W., & Ye, J. P. (1996). Clinical observation of efficacy of immunotherapy combined with rhinitis nasal irrigation for perennial allergic rhinitis [Mianyi liaofa hebing biyan chongji zhiliao changnianxing bianyingxing biyan liaoxiao guancha]. *Chinese Journal of Otorhinolaryngology of Integrated Traditional and Western Medicine [Zhongguo Zhongxiyi Jiehe Erbiyanhouke Zazhi]*, 4(2), 69-71.
55.	Zhang 2007b	Zhang, Y. (2007). 103 cases pf perennial allergic rhinitis treated with Jianbi mixture [Jianbiheji zhiliao changnianxing bianyingxing biyan 103 li liaoxiao guancha]. *Chinese Journal of Information on Traditional Chinese Medicine [Zhongguo Zhongyiyao Xinxi Zazhi]*, 14(7), 58-59.
56.	Zhao 2012	Zhao, Y. (2012). The curative effect of Tongqiaobiyankeli on allergic rhinitis [Tongqiaobiyankeli zhiliao guominxing biyan de liaoxiao guancha]. *Contemporary Medicine [Dangdai Zhongyi]*, 18(295), 136-137.

No.	Study I.D.	Included RCTs
57.	Zhao 2009	Zhao, Y., Woo, K. S., van Hansselt, C. A., Wong, K. W., Cheng, K. F., Lam, C. W. K., & Leung, P. C. (2009). Treatment of perennial allergic rhinitis using Shi-Bi-Lin, a Chinese herbal formula. *Journal of Ethnopharmacology*, 122, 100-105.
58.	Zheng 2007	Zheng, J., & Luo, H. Y. (2007*). Clinical observation of the effect of Chinese traditional medicine Xingbiningjiaoji in children allergic rhinitis [Zhongyao xingbi ningjiaoji zhiliao xiao'er bianyingxing biyan linchuang liaoxiao guancha]*. (Masters), Fujian College of Traditional Chinese Medicine, Fujian, China.
59.	Zhong 2013	Zhong, R. Q. (2013). *Clinical study on carminative Tongqiao soup treatment of perennial allergic rhinitis*. (Masters), Beijing University of Chinese Medicine, Beijing, China.
60.	Zhou 2001b	Zhou, P. M., Zhang, Z. H., He, G., Wang, X., Yin, M., Chen, W., . . . Du, P. (2001b). Clinical observation of 93 cases of allergic rhinitis using Xinzhi naristillae [Xinzhi dibiji zhiliao bianyingxing biyan 93 li linchuang guancha]. *Chinese Journal of Traditional Medical Science and Technology [Zhongguo Zhongyiyao Keji]*, 8(4), 254-255.
61.	Zhou 2005	Zhou, S. J., & Xie, Y. M. (2005). Clinical observation of integrative medicine in treatment of allergic rhinitis [Zhongxiyi jiehe zhiliao bianyingxing biyan liaoxiao guancha]. *Journal of Guangdong College of Pharmacy [Guangdong Yaoxueyuan Xuebao]*, 21(3), 372-373.
62.	Zou 2012	Zou, W. Q., Niu, Q. Y., Liu, X. R., & Xing, W. D. (2012). 52 deficient cases of allergic rhinitis treated with Tuomintongqiao capsules [Tuomintongqiao jiaonang zhiliao qixuxing guominxing biyan 52 li linchuang guancha]. *Yunnan Chinese Medicine Journal [Yunnan Zhongyiyao Zazhi]*, 33(6), 36-37.

5.2. Characteristics of included studies

5.2.1. Design of studies

All the 62 clinical studies were claimed as RCTs. The majority of them (59 studies) employed two-arm design whilst only three Chinese studies used three-arm (Chen 2004; Xie 2009; Zhang 1996) and one in four-arm trial (Xiao 2015). There was no cross-over clinical trial included.

Forty-three out of 62 trials were single centre studies. Nine RCTs were multicentre clinical trials, five trials in two centres (Gao 2009; Lenon 2012; Lu 2011; Peng 2004; Wu 2012a), two trials in three centres (Wu 2009; Zhao 2009), one trial in four centres (Zou 2012) and one in 62 centres (Baba 1995). Six studies did not provide sufficient information (Cao 2007; Hong 2005; Lu 1998; Peng 2001; Xie 2009; Zhang 1996). Although the rest of four papers did not report the details, the trials were most likely performed in one centre as three of them only had one author completed the trials (Jiang 1997; Li 2008; Xin 2005) and two authors in the other trials were from the same hospital (Liu 2004).

More than one eighth of the included studies (11 out of 62) were supported by at least one external funding such as funded by national, provincial, local government, hospital or university grants (Huang 2010; Jung 2011; Lenon 2012; Liu 2001; Lu 2011; Qiu 2012; Tang 2008; Wang 2000a; Wu 2009; Zhao 2009; Zheng 2007). Two trials were partially supported by the pharmaceutical manufacturers (Baba 1995; Xue 2003b). The other 49 studies did not report the funding sources.

5.2.2. Sample sizes

The sample sizes of the included studies were various, ranging from 20 to 564 participants with an average of 106 participants per trial. Thirty-seven trials had sample sizes between 20 and 100 (both inclusive). Seventeen studies had sample sizes over 100 but less than 200 (Chen 2014;

Chen 2004; Gao 2009; Hong 2005; Huang 2006b; Lin 2013; Liu 2001; Lu 1998; Lu 2003; Lu 2011; Luo 2013; Shen 2004; Wu 2009; Wu 2012a; Xie 2009; Zhao 2009; Zou 2012). There were eight studies with sample sizes that exceeded 200 (Baba 1995; Guo 2010; Qiu 2012; Shi 2012; Xiao 2015; Yan 2011; Zhang 2007; Zhou 2005).

5.2.3. Setting

Among 62 trials, 51 studies were performed in mainland China and eleven studies were conducted outside mainland China, including four in Australia (Hu 2002; Lenon 2012; Xue 2003a; Xue 2003b), one in Croatia (Matkovic 2010), one in Hong Kong (Zhao 2009), one in Japan (Baba 1995), two in Taiwan (Jiang 2012; Liu 2010), one in South Korea (Jung 2011) and one in Switzerland (Zhao 2010).

Thirty-two studies clearly indicated that only outpatients enlisted from hospitals participated in the trials. Patients in four trials were recruited solely from outpatient clinics, three trials in Australia (Lenon 2012; Xue 2003a; Xue 2003b) and one in Switzerland (Zhao 2010) respectively. Only one study stated that both outpatients and inpatients were included in the trial (Hong 2005). Only Bao 2013 cited participants were recruited from inpatients of hospital. Fifteen studies did not mention whether outpatients or inpatients were involved however, they indicated that the patients were recruited from hospitals, including one in Australia (Hu 2002), one in Japan (Baba 1995), one in South Korea (Jung 2011), one in Hong Kong (Zhao 2009) and eleven in mainland China (Cao 2014; Chen 2012; Chen 2014; Liu 2001b; Lu 1998; Shi 2012; Sun 2014a; Qin 2006; Qiu 2012; Wu 2012; Zou 2012). Nine studies conducted in mainland China did not specify where the participants were recruited from, outpatients or inpatients (Cao 2007; Chen 2004; Jiang 1997; Li 2008; Liu 2004; Peng 2001; Xie 2009; Xin 2005; Zhang 1996).

5.2.4. Types of participants

The included studies randomised 8,470 participants and analysed 8,395. Their ages ranged from two to 82 years. Two studies did not clearly report the ages of participants (Huang 2006b; Zhang 2007b). Three studies only indicated the mean of the participants' ages and the range of ages was not provided (Lenon 2012; Matkovic 2010; Wu 2012a).

Nine studies included children only (Cao 2014; Chen 2012; Li 2012c; Lin 2013; Lu 1998; Lu 2011; Luo 2013; Wu 2009; Zheng 2007) and 30 studies focused on adults only (Bao 2013; Cao 2007; Chen 2011; Chen 2014; Han 2002; Hong 2005; Hu 2002; Huang 2008a; Jiang 1997; Jin 2010; Jung 2011; Li 2012b; Liang 2011b; Lenon 2012; Liu 2004; Matkovic 2010; Peng 2001; Peng 2004; Shi 2014; Tang 2008; Wu 2012; Xiao 2015; Ye 2015; Xin 2005; Xue 2003a; Xue 2003b; Zhang 2007; Zhao 2009; Zhong 2013; Zhou 2005). Twenty-three studies mixed the children and adults (Baba 1995; Chen 2004; Gao 2009; Guo 2010; Huang 2010; Jin 2010; Li 2008; Liu 2001; Lu 2003; Lu 2009; Qin 2006; Qiu 2012; Shen 2004; Shi 2012; Sun 2014a; Wang 2000a; Xie 2009; Yan 2011; Yang 2004; Zhang 1996; Zhao 2012; Zhou 2001b; Zou 2012).

For the included studies conducted in mainland China, 56 out of 62 diagnosed their participants according to Chinese Medical Association's Criteria for Allergic Rhinitis which were developed in 1990 and further revised in 1997 and 2004. Only four of them adopted the diagnostic criteria specified in the textbooks (Bao 2013; Li 2012c; Sun 2014a; Zhou 2005). Two studies (Lenon 2012; Liang 2011) performed outside of China developed their own diagnostic criteria. All the diagnostic criteria included a number of signs and symptoms as well as one objective test (e.g. skin prick test or a specific IgE test) to determine participants' allergy.

Twenty-eight of them investigated the effects of CHMs for patients with PAR (Baba 1995; Bao 2013; Chen 2004; Hu 2002; Huang 2008; Huang 2010; Jiang 1997; Jin 2010; Jung 2011; Li 2008; Liang 2011b; Lin 2013; Liu 2001; Lu 2009; Lu 2011; Peng 2004; Qin 2006; Shi 2012; Shi 2014; Tang 2008; Xie 2009; Xin 2005; Yan 2011; Zhang 1996; Zhang 2007b; Zhao 2009; Zhong 2013; Zou 2012) and five studies focused on patients with SAR only (Lenon 2012; Matkovic 2010; Qiu 2012; Xue 2003a; Xue 2003b). Three studies indicated both SAR and PAR patients were recruited in the trials (Hong 2005; Li 2012; Shen 2004). The rest 26 studies did not specify SAR or PAR and they may include both types of AR.

Most included studies did not differentiate the AR syndromes when recruiting participants. Only 24 studies adopted differential diagnosis according to CM theories and applied a fixed formula to treat patients with a particular syndrome. Ten of them focused on Lung and Spleen Qi deficient syndromes (Cao 2014b; Chen 2012; Chen 2014; Li 2012c; Li 2012b; Qin 2006; Qiu 2012; Shi 2014; Yan 2011; Zou 2012), five for Lung Qi deficiency (Lin 2013; Lu 2011; Shi 2012; Sun 2014a; Zhang 2007b), two for Spleen Qi deficiency (Liang 2011; Tang 2008), one for phlegm retention (Gao 2009), four for Lung Qi deficient cold type (Bao 2013; Huang 2008; Zhao 2012; Zhong 2013), and two for heat in Lung meridian syndrome (Jin 2010; Luo 2013). Three studies recruited patients with any syndromes of AR but treated them individually with modified Chinese herbal formulae according to their syndromes (Li 2008; Lu 2009; Zhou 2005).

5.2.5. Types of interventions

A total of 62 CHMs were evaluated in the treatment groups. Three studies used single Chinese herbs, including fermented red ginseng (*Ginseng et Rhizoma Radix Rubra*) (Jung 2011), Huang Qi (*Astragali Radix*) (Matkovic 2010), and volatile oil of *Magnoliae Flos* (Xin Yi) (Wu 2009). The rest of 59 included studies used 59 different Chinese medicinal formulae, consisting of 564

Chinese herbs, in the treatment groups. Five trials (Liang 2011; Cao 2014, Li 2012b; Huang 2010 and Ye 2015) used two formulae; while Li 2012a and Lu 2009 employed three formulae for three different syndromes.

The forms of Chinese herbs used in these included studies were various, orally (decoction, capsule, granule or liquid) and/or externally (nasal drop or spray). Fifty-three studies adopted oral administration only. Twenty-four of them used formulae in the decoction form (Chen 2011; Chen 2014; Gao 2009; Hong 2005; Huang 2008a; Jiang 1997; Jin 2010; Li 2008; Li 2012b; Li 2012c; Liang 2011b; Liu 2001; Lu 1998; Lu 2003; Lu 2009; Lu 2011; Luo 2013; Qiu 2012; Peng 2001; Tang 2008; Yan 2011; Zhang 2007b; Zhong 2013; Zhou 2005). Sixteen studies applied the granule form of CHMs in the treatment group (Baba 1995; Cao 2007; Chen 2004; Huang 2010; Lenon 2012; Liang 2011b; Lin 2013; Liu 2010b; Matkovic 2010; Peng 2004; Qin 2006; Shen 2004; Xie 2009; Yang 2004; Zhang 1996; Zhao 2012). The formulae in 11 studies were in the capsule form (Cao 2014b; Han 2002; Hu 2002; Jung 2011; Shi 2012; Sun 2014a; Wu 2012; Xue 2003a; Xue 2003b; Zhao 2009; Zou 2012). Two studies (Guo 2010; Bao 2013) used the oral liquid form of Chinese herbs. Four studies used CHMs externally in nasal drop form (Huang 2006; Liu 2004; Wang 2000a; Wu 2009) and four trials employed nasal spray (Chen 2012; Zhang 1996; Zheng 2010; Zhou 2001b). The Xin 2005 study applied both decoction and nasal droplet forms of CHMs for treatment.

The interventions in control groups consisted of placebo (seven trials), WM (e.g. anti-histamine drugs) (48 trials), immunotherapy (two trials), surgery (one trial), radiofrequency (two trials), and acupuncture (two trials). The most commonly used anti-histamine drugs were Cetirizine, Loratadine or Desloratadine, Hismanal and Chlorphenamine maleate tablets.

When co-intervention was not involved in the trials, seven studies compared CHM with placebo (Baba 1995; Hu 2002; Jung 2011; Lenon 2012; Matkovic 2010; Xue 2003a; Zhao 2009). Another 37 studies compared CHMs with Western medicine as control. Among them, 27 studies compared CHM with oral WM (Bao 2013, Cao 2007; Chen 2014; Gao 2009; Guo 2010; Han 2002; Hong 2005; Huang 2008a; Huang 2010; Jiang 1997; Jin 2010; Liang 2011b; Liu 2001; Lu 2011; Luo 2013; Peng 2001; Peng 2004; Qin 2006; Qiu 2012; Shen 2004; Sun 2014a; Yan 2011; Yang 2004; Ye 2015; Zhang 1996; Zhang 2007b; Zhong 2013); only one (Wu 2009) used nano-liposome nasal drops for the control, whilst there were six studies which used nasal sprays as a comparator (Chen 2012; Huang 2006b; Wang 2000a; Zheng 2007; Zhou 2001b; Zou 2012); one trial (Xin 2005) involved CHM oral plus external versus WM oral plus nasal spray as comparators; and two studies compared CHM with radiofrequency (Chen 2004; Xie 2009).

When co-interventions were involved in the included RCTs, 17 studies plus one comparison from three multi-arm RCTs (Chen 2014; Xie 2009; Zhang 1996) evaluated the additional effects of CHMs. Chen 2014 and Xie 2009 compared Chinese herbs plus radiofrequency with same radiofrequency alone and Zhang 1996 compared Chinese herbs plus immunotherapy with same immunotherapy alone.

Among 17 studies, six used both oral and external applications of WM in the control group (Li 2008; Li 2012c; Lin 2013; Lu 2003; Lu 1998; Shi 2012). Lu 2009 compared CHM plus WM spray with WM sprays only. Xiao 2015 conducted a four-arm trial, two comparisons relevant to this review were evaluated: one was to compare effects of Chinese herbal decoction plus acupuncture with WM (oral and external) and the same acupuncture with WM; the other was to compare CHM with WM (oral and external) versus the same WM alone. When used externally in the nasal cavity, one study compared Chinese herbal drops plus surgery with same

surgery procedure (Liu 2004b). The rest of the studies compared CHM with WM oral versus the same WM (Cao 2014b; Chen 2011; Li 2012b; Shi 2014; Tang 2008; Wu 2012a; Zhao 2012; Zhou 2005).

Treatment periods in the included studies varied from two weeks to three months. All the included trials followed up the participants until the end of the treatments. Follow-up periods after treatment ranged from two weeks to one year. Nine studies followed up the patients for one year (Chen 2004; Han 2002; Hu 2002; Jin 2010; Liu 2001; Lu 2003; Peng 2004; Zhang 1996; Zhou 2005). Six studies (Hong 2005; Huang 2010; Shi 2012; Xiao 2015; Ye 2015; Zhong 2013) followed up for six months. Zheng 2007 followed up to four months. Another two studies (Cao 2007; Luo 2013) followed up patients for three months. The follow-up period of the Lu 1998, Lin 2013; Wu 2012a and Xie 2009 trials were two months. Four studies (Li 2012b; Liang 2011; Qiu 2012; Xin 2005) followed up the patients for one month. Qin 2006 followed up to three weeks while Bao 2013; Gao 2009 and Xue 2003b only followed up for two weeks. Thirty trials did not provide information on follow-up. Two trials indicated that long-term follow-up was applied however, no details were stated (Zhang 1996; Zhou 2005).

5.2.6. Types of outcome measures

All the included studies involved in one or more primary and/or secondary outcome measures. For the purpose of evaluation, the last treatment is defined as immediate follow-up, one week (inclusive) to six months (exclusive) after the last treatment as short-term follow-up, six months (inclusive) to 12 months (exclusive) after the treatment period as intermediate-term follow-up. Long-term follow-up is regarded as one year or above after treatment. There are five outcome measures reported as follows:

i. Improvement of symptoms

Majority of included studies assessed the immediate, short-term, intermediate-term and/or long-term effects on the improvement of global symptoms (by effective rates) and severity of symptoms (by individual symptom scores, and/or total symptom scores).

Twenty-seven studies used an effective rate to show the immediate effects of global symptom improvement by comparing the symptom scores before and after treatment (Baba 1995; Bao 2013; Cao 2014b; Chen 2011; Chen 2012; Chen 2014; Gao 2009; Guo 2010; Huang 2008a; Li 2008; Lu 2009; Lu 2011; Peng 2001; Qin 2006; Shen 2004; Shi 2014; Sun 2014a; Tang 2008; Wang 2000a; Wu 2009; Xin 2005; Yan 2011; Yang 2004; Zhang 2007; Zhao 2012; Zhou 2001b; Zou 2012). Four trials (Hu 2002; Yan 2014; Yang 2004; Zhao 2009) did not apply any scales/scores to examine the improvement of symptoms. Lenon 2012; Xue 2003a and Xue 2003b rated patients' overall response to treatment according to a seven-point scale at the end of treatment period. Lenon 2012 also rated global symptoms according to a five-point scale in their studies. Four trials (Hu 2002; Yan 2014; Yang 2004; Zhao 2009) did not apply any scales or scores to examine the improvement of symptoms.

Seventeen trials evaluated the short-term effects. Three trials rated at two weeks after the last treatment (Bao 2013; Gao 2009; Xue 2003b), while one trial rated three weeks after treatment (Qin 2006). Five trials evaluated at one month after the treatment period (Chen 2014; Li 2012b; Liang 2011b; Qiu 2012; Xin 2005). Four trials assessed at two months after Chinese herbal treatment (Lin 2013; Lu 1998; Wu 2012a; Xie 2009). The Zhang 1996 conducted a three-arm trial in which the investigators rated one of study for four months, while another of Zhang 1996 was assessed for one year. The immunotherapy treatment for the one-year evaluation was completed at eight months. Two trials were rated three months after treatment (Cao 2007; Luo 2013). Only Zheng 2007 conducted follow-up four months after treatment. Intermediate-term

evaluation (six months after treatment) was performed in six trials (Hong 2005; Huang 2010; Shi 2012; Xiao 2015; Ye 2015; Zhong 2013). Nine studies assessed the long-term (one year after treatment) effects (Chen 2004; Han 2002; Hu 2002; Jin 2010; Lin 2013; Liu 2001; Lu 2003; Peng 2004; Zhou 2005). The rest of the studies conducted immediate follow-up after treatment.

Owing to the variety of the criteria for evaluating this outcome, the Chinese medicinal formulae were rated as effective if the effective rate was greater than 20%. The effective rate was calculated as (scores before treatment – scores after treatment) /scores before treatment x 100%.

The severity of symptoms was reported as the individual symptom scores and/or the total symptom scores. The individual symptom scores were presented as mean ± standard deviation (SD) for immediate effects in nine trials (Chen 2014; Jung 2011; Lu 2011; Matkovic 2010; Shi 2014; Wu 2009; Zhao 2009; Zheng 2013; Zou 2012) and short-term effects in eight studies (Bao 2013; Cao 2007; Gao 2009; Lenon 2012; Liu 2004b; Lu 1998; Peng 2001; Qin 2012). The Peng 2004 study showed the findings with the reduction of scores. Two studies illustrated the findings as total scores for immediate (Hu 2002; Liu 2004b), two trials for intermediate effects (Huang 2010; Zhong 2013) and one for long-term effects (Hu 2002). Total symptom scores by mean ± SD were reported for immediate effects in 10 trials (Gao 2009; Huang 2008a; Jung 2011; Liu 2001; Matkovic 2010; Wang 2006b; Xue 2003a; Xue 2003b; Zou 2012; Zhong 2013). The Jiang 1997 studies listed the number and percentage of patients with decreased scores in individual symptoms. Out of 62 studies, only Chen 2012 conducted lab tests to assess IgE and IL4 values.

ii. Quality of life

Six studies assessed the CHM effects on quality of life using RQLQ or mini-RQLQ with presentation of results in mean ± SD (Hu 2002; Jung 2011; Lenon 2012; Matkovic 2010; Xue 2003a; Xue 2003b), or SF-36 by mean ± SD in Gao 2009, or percentage of changes in scores in Zhao 2009.

iii. Medication consumption

Five trials counted rescue medication consumption (Hu 2002; Lenon 2012; Xue 2003a; Zhao 2009). However, three trials Hu 2002, Lenon 2012 and Xue 2003a reported the percentage of improvement of extra medication scores. The Xue 2003b and Zhao 2009 studies only stated that they recorded the relief medications but no scores were reflected.

iv. Serum IgE level

Eleven studies tested total serum IgE level, nine for immediate effects (Chen 2012; Hu 2002; Jung 2011; Liu 2010b; Matkovic 2010; Xue 2003a; Zhang 1996; Zhao 2009; Zhou 2001b); one study evaluated for short-term effects (Zhang 1996) and one for long-term effects (Han 2002). Among them, the Matkovic 2010, Xue 2003a and Zhao 2009 studies did not provide any data. The Zhou 2001b trial only reported results for 26 out of 93 patients in the treatment group. The Zhang 1996 study examined serum IgE immediately after two-month CHM treatment whilst the immunotherapy was not finished. Data were only provided for CHM group with the comparator measurement.

v. Adverse events

Thirty trials provided information on adverse events. An adverse event is regarded as a minor case when the patient was still able to complete the trial. In the same vein, an adverse event is considered as a major case when the patient had to withdraw from the trial due to the unpleasant

reactions. All the withdrawn cases are categorised as major cases even if the reasons of withdrawal were not provided. Most of reported adverse events were minor cases.

Fifteen studies found adverse events in both treatment and control groups (Baba 1995; Bao 2013; Chen 2014; Han 2002; Hu 2002; Huang 2008a; Jung 2011; Lenon 2012; Lu 1998; Peng 2004; Wang 2000a; Xue 2003a; Xue 2003b; Zhao 2009; Zhou 2001b). Among them, Huang 2008a trial did not provide any data. Five trials did not observe any adverse events in treatment group but some in control groups (Gao 2009; Guo 2010; Huang 2010; Luo 2013; Shen 2004). The investigators in Chen 2004, Hong 2005, Liang 2011b, Shi 2014, Sun 2014a, Xie 2009, Zhong 2013 and Zou 2012 studies observed no adverse events during the trial periods. Adverse events in the treatment group were noted in one study (Lu 1998) but no information was provided on the control group. Matkovic 2010 and Shi 2014 did not specify the adverse events stated in the trials for each group. The Wu 2009 study generally described the adverse events; however, no details were reported. The rest of 32 studies did not report the adverse events.

5.3. Assessment of risk of bias

The risk of bias of each included study was evaluated according to the criteria listed in 4.1.4. The graph and summary of "risk of bias" assessment are illustrated in Figure 10 and Figure 11 respectively. Each aspect of the risk of bias assessment is detailed from 5.3.1 to 5.3.5.

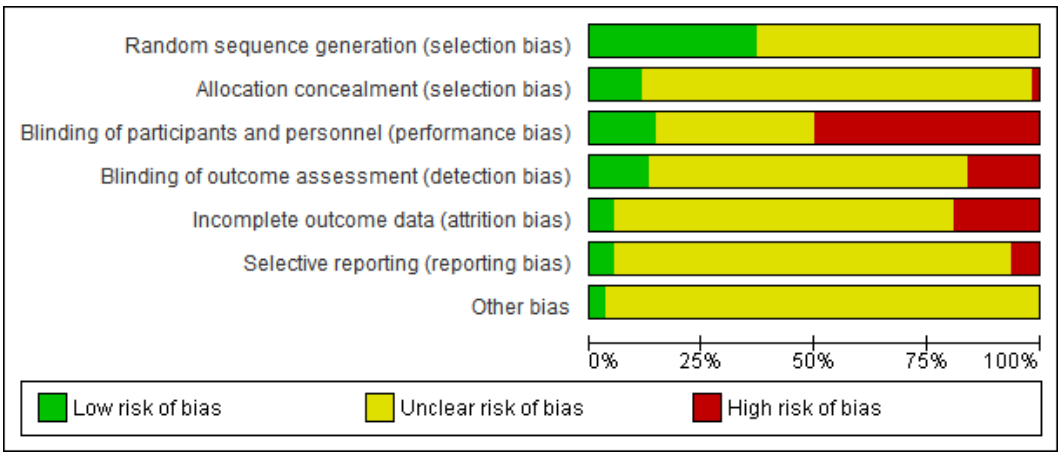


Figure 10. Graph of risk of bias of 62 included RCTs

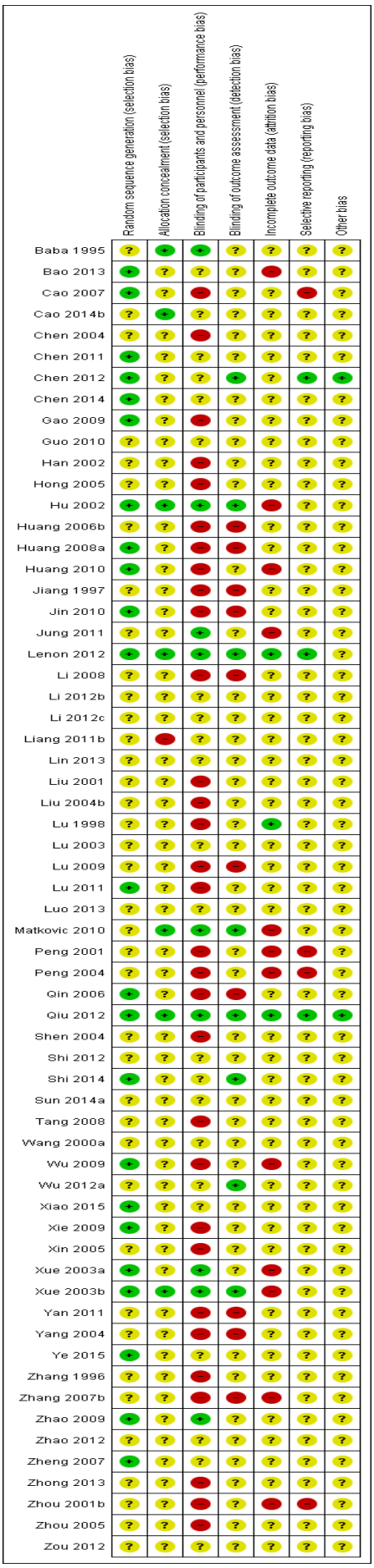


Figure 11. Summary of risk of bias of 62 included RCTs

5.3.1. Allocation (selection bias)

All the included studies reported that participants were randomly assigned into treatment and control groups. Nineteen out of 62 studies provided randomisation allocation methods. Random number table was listed as a means of randomised allocation in 10 trials (Bao 2013; Chen 2011; Chen 2012; Chen 2014; Huang 2010; Jin 2010; Qin 2006; Qiu 2012; Wu 2009; Xie 2009), the computer-generated random number in nine studies (Bai 2012; Cao 2007; Gao 2009; Hu 2002; Jiang 2012; Liu 2001; Xue 2003a; Xue 2003b; Zhao 2009).

In terms of ratio, 1:1 ratio randomisation was used in 17 studies (Bao 2013; Cao 2007; Cao 2014b; Gao 2009; Huang 2008a; Li 2012b; Li 2012c; Lin 2013; Lu 2011; Luo 2013; Shi 2014; Shi 2012; Sun 2014a; Wu 2012a; Zhao 2012; Zhong 2013, Zou 2012), 1:1:1 ratio randomisation in one trial (Liang 2011b) and 2:1 ratio randomisation in one study (Matkovic 2010). Two studies (Huang 2006b; Lu 2011) indicated that stratified randomisation was used however no further details were provided. Only one study reported the method for concealment of allocation that is, using sealed envelopes to allocate the random numbers to participants (Shi 2012). The rest of 40 trials did not describe the methods used for performing randomisation.

5.3.2. Blinding (performance bias and detection bias)

Eight studies employed double-blinding (Baba 1995; Hu 2002; Jung 2011; Lenon 2012; Matkovic 2010; Xue 2003a; Xue 2003b; Zhao 2009) and only one study used single-blinding (Cao 2014b) strategy. Two studies clearly indicated that no blinding was employed in the trial (Qin 2006; Bao 2013). The rest of 52 studies did not provide any information on blinding.

Seventeen studies (Bai 2012; Cao 2014b; Huang 2008a; Jiang 1997; Jin 2010; Li 2008; Li 2012b; Li 2012c; Liang 2011b; Lin 2013; Lu 2009; Luo 2013; Sun 2014a; Yan 2011; Yang 2004; Zhang 2007b; Zhao 2012) only had one author for their published papers and six studies

were research work for Masters or PhD degrees with single authors (Chen 2012a; Gao 2009; Liu 2010b; Qin 2006; Qiu 2012; Zhong 2013). It is impossible for one investigator to perform blinding for treatment and outcome assessment.

5.3.3. Incomplete outcome data (attrition bias)

The attrition bias was only assessed for the immediate effects. Majority of studies (61 out of 62) had the same number of participants randomised and analysed in the results for the global symptom improvement. Among them, only Lu 1998 study clearly stated that all the 105 participants completed the trial which indicated that there were no missing data. Only Wu 2009 reported the results of laboratory tests for part of participants.

Fourteen trials reported a total of 111 withdrawals/drop-outs (Baba 1995; Cao 2014b; Gao 2009; Hu 2002; Huang 2010; Jung 2011; Lenon 2012; Liang 2011b; Matkovic 2010; Wu 2012a; Xue 2003a; Xue 2003b; Zhang 2007; Zhao 2009). All except three studies (Lenon 2012; Liang 2011; Zhao 2009) provided reasons for withdrawals/drop-outs, including loss of follow-up, withdrawal of consent, discontinued treatment, side effects of interventions and poor compliance. However, only six studies applied the intention-to-treat method to their data analysis (Hu 2002; Lenon 2012; Matkovic 2010; Xue 2003a; Xue 2003b; Zhao 2009) and the rest did not address the missing data in the analysis.

5.3.4. Selective reporting (reporting bias)

None of the included studies reported their protocol prior to publishing their clinical trials; therefore it is unclear if the included studies selectively reported the results. In the SR, the data in the results of the included studies were compared with those in methods section to determine if selective reporting existed. Selective reporting may be involved in three trials as they stated

that a certain number of patients with completed data were reported (Cao 2007; Peng 2001; Peng 2004).

5.3.5. Other potential sources of bias

A total of 55 studies exhibited a significant baseline imbalance in participants' age during allocation and were rated with "unclear risk" for allocating participants of mixed ages from six to 76 years. Only seven studies (Baba 1995; Hu 2002; Jung 2011; Lenon 2012; Matkovic 2010; Xue 2003a; Xue 2003b) recruited adults from 18 years of age onwards for selection of studies. In the funding of the projects, external grants supported 11 trials. All but three trials (Lenon 2012; Liu 2001; Xue 2003b) reported that CHMs were more effective than comparators. One trial stated an equal efficacy to the comparator used in the study (Jiang 1997). The high rate of reporting positive effects of CHMs may be biased with contribution from the external funding.

5.4. Clinical effects of CHM for AR

5.4.1. CHM versus placebo

In this category of comparison, seven trials compared oral administration of CHM with placebo (Baba 1995; Hu 2002; Jung 2011; Lenon 2012; Matkovic 2010; Xue 2003a; Zhao 2009).

i. Improvement of symptoms

Among seven studies, the physicians in the Hu 2002 and Zhao 2009 studies evaluated the patients' overall improvement without using any scales/scores. Thus, their results were not included in the meta-analysis. The Baba 1995 trial used an effective rate to evaluate the immediate global symptom improvement according to the change of the severity of symptoms. The Chinese herbal group was more effective than the placebo group (RR 1.97; 95% CI 1.47 to 2.65).

Two studies assessed severity of nasal symptoms (Jung 2011; Xue 2003a), only Xue 2003a rated patients' overall response to treatment using a seven-point scale instead of changed scores before and after treatment. When *post hoc* analysis was applied, both Jung 2011 and Xue 2003a studies depicted significant difference for CHM when assessed by patients (SMD -0.61; 95% CI -1.00 to -0.22). The heterogeneity was nil (I^2 = 0%) (Figure 12).

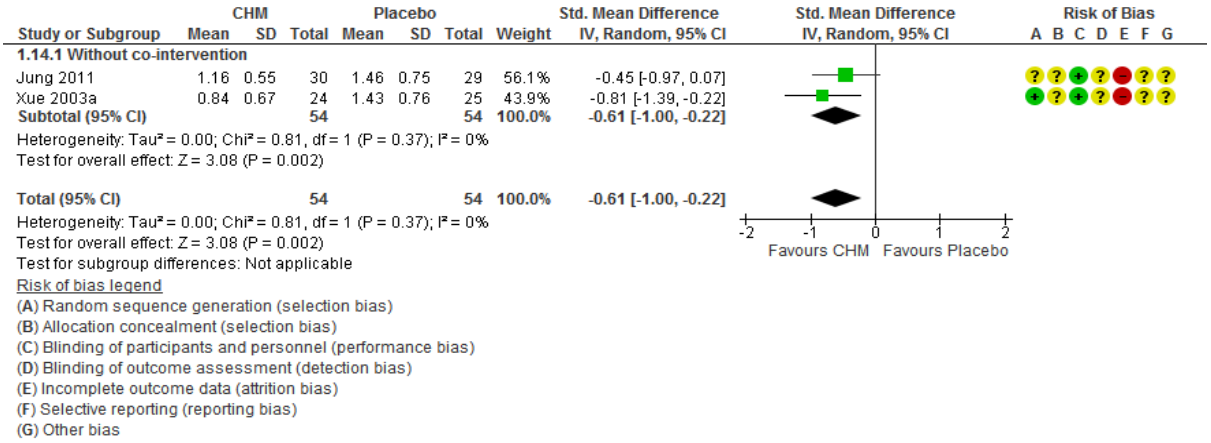


Figure 12. Severity of nasal symptoms (assessed by patients, immediate follow-up *post hoc* analysis) for CHM versus placebo

Patients in three studies (Lenon 2012; Xue 2003a; Jung 2011) assessed the severity of their nasal symptoms in immediate follow-up of their treatment. No significant results between two groups were demonstrated (SMD -0.38; 95% CI -0.85 to 0.09). Heterogeneity was substantial (I^2 = 63%) (Figure 13).

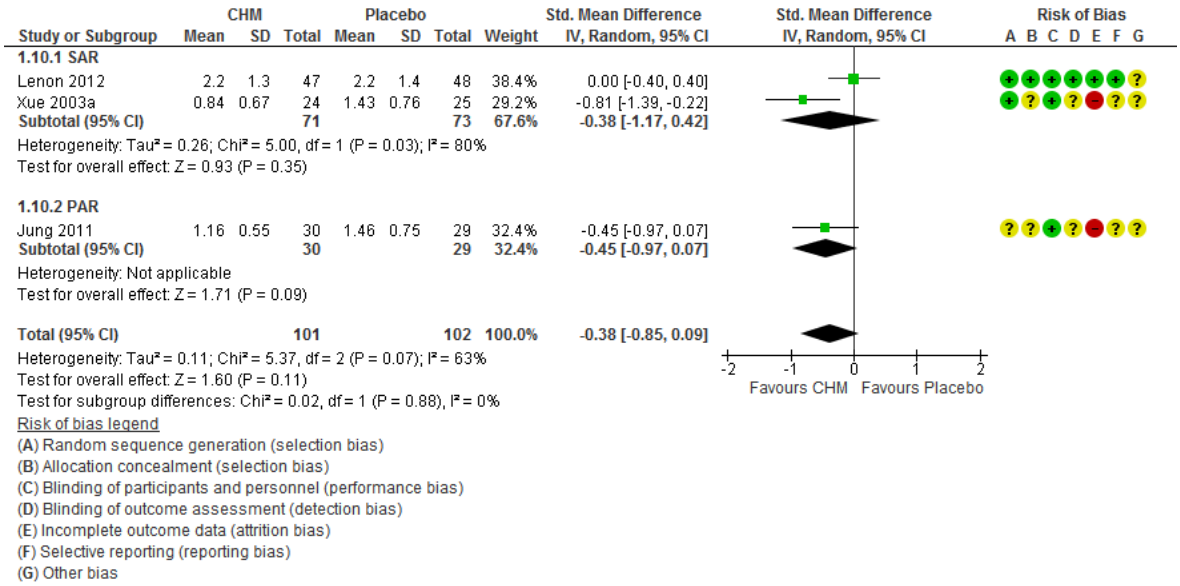


Figure 13. Severity of nasal symptoms (assessed by patients, immediate follow-up) for CHM versus placebo

Two trials (Hu 2002; Matkovic 2010) presented the changes in sneeze and runny nose scores at the immediate follow-up which favoured CHM for sneezing. The pooled data showed that the Chinese herbs were more effective than placebo for relieving sneeze (SMD 0.79; 95% CI 0.36 to 1.22) (Figure 14) but not for runny nose (SMD 0.62; 95% CI -0.10 to 1.35). The heterogeneity for the latter was substantial (I^2 = 65%) (Figure 15).

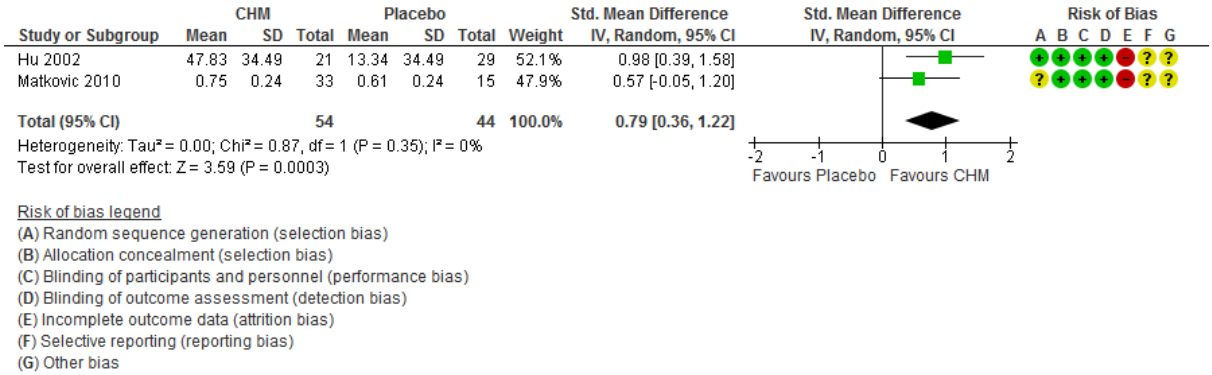


Figure 14. Changes in sneeze score (immediate follow-up) for CHM versus placebo

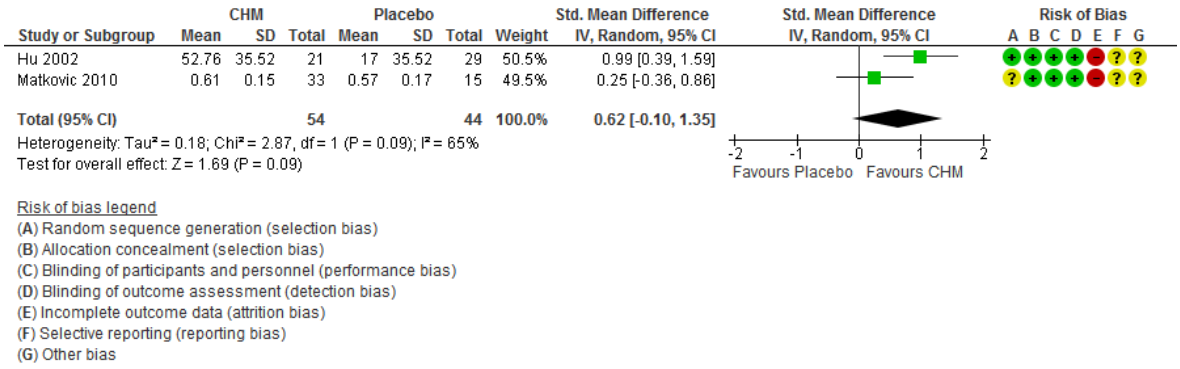


Figure 15. Changes in runny nose (immediate follow-up) for for CHM versus placebo

The Hu 2002 study also illustrated that Chinese herbs significantly reduced more scores of nasal congestion (MD 27.92; 95% CI 12.24 to 43.60), itchy nose (MD 0.98; 95% CI 0.39 to 1.58) and itchy eyes (MD 28.33; 95% CI 12.42 to 44.24) than placebo at the end of 12-week treatment.

The Zhao 2009 trial reported the individual symptom scores after four weeks' treatment. Significant difference between two groups was only shown in itchy ears with a favour towards placebo (MD 0.34; 95% CI 0.06 to 0.62). Symptoms recurred in the placebo group except for nasal congestion in the CHM group (Shi-Bi-Lin) were still decreasing. However, no detailed data were available. Meta-analysis was not applied to these outcomes.

In addition, the Hu 2002 study further assessed the changes in individual symptom scores for long-term effects (one year after treatment). The authors claimed changes in runny nose (MD 27.51; 95% CI 11.37 to 43.65) and sneeze score (MD 24.85; 95% CI 7.21 to 42.49) in Biminne group were more significant than placebo group.

Three trials evaluated the patient-rated for severity of nasal symptom score (Jung 2011; Lenon 2012; Xue 2003a). CHM and placebo had no significant difference in the outcome measure (SMD -0.38; 95% CI -0.85 to 0.09). The heterogeneity was substantial (I^2 = 63%) (Figure 16).

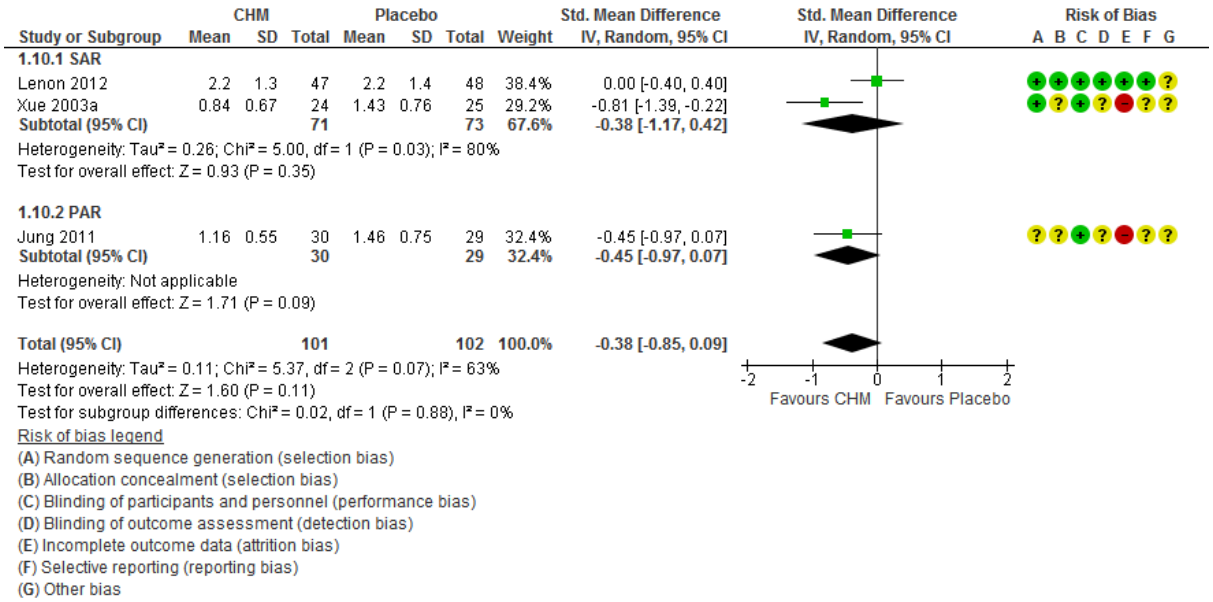


Figure 16. Severity of nasal symptoms (assessed by patients, immediate follow-up) for CHM versus placebo

The specialist-rated total nasal symptom scores in Xue 2003a favoured CHM (MD -0.60; 95% CI -1.02 to -0.18). For non-nasal symptoms assessed by specialist, no significant difference was also detected (MD -0.30; 95% CI -0.65 to 0.05). Similarly, no significant difference for CHM and placebos was demonstrated when assessed by patients for their non-nasal symptoms (MD -0.28; 95% CI -0.64 to 0.08).

The Matkovic 2010 study assessed the global symptom scores for SAR which indicated that Huang Qi (*Astragali Radix*) was less effective than placebo at the end of six-week treatment (MD 0.77; 95% CI 0.62 to 0.92).

ii. Quality of life

All seven studies except Baba 1995 evaluated quality of life. RQLQ/mini-RQLQ was popularly used in five studies (Hu 2002; Jung 2011; Lenon 2012; Matkovic 2010; Xue 2003a). Only the Zhao 2009 trial used SF-36 questionnaire.

The changes in overall RQLQ scores at the immediate follow-up from three studies (Hu 2002; Jung 2011; Matkovic 2010) were pooled. The meta-analysis showed the Chinese herbs and placebo had similar effects on the change of RQLQ scores (SMD 0.11; 95% CI -0.14 to 0.36). No heterogeneity was reflected (I^2 = 0%). The changed scores in each domain could not be compared for these three studies due to lack of data. The Hu 2002 trial also followed up with RQLQ after one year of treatment. There was no significant difference between two groups (Figure 17). However, no detailed data were provided.

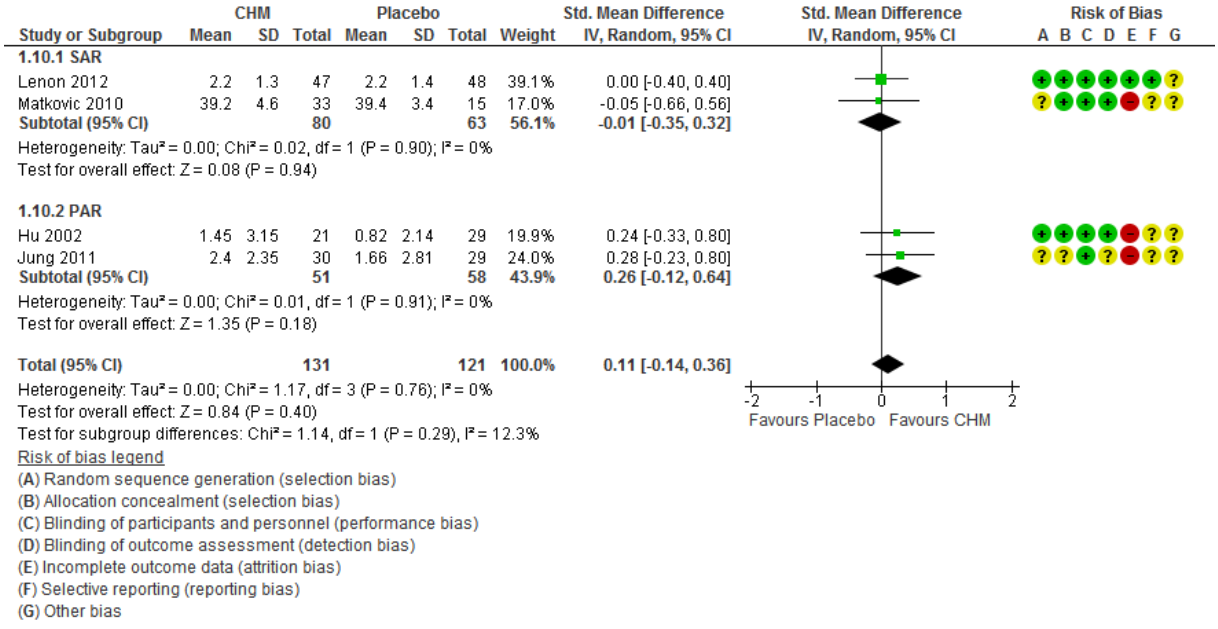


Figure 17. Changes in total RQLQ score (immediate follow-up) for CHM versus placebo

At the end of eight-week treatment, Xue 2003a compared the total scores for RQLQ Section One (symptoms and activities related to SAR) and RQLQ Section Two (impact of SAR on emotional aspects). Placebo was statistically significant for RQLQ Section One (MD -0.66;

95% CI -1.20 to -0.12), however RQLQ Section Two (MD 1.00; 95% CI 0.30 to 1.70) proved CHM had an effect.

The Zhao 2009 trial compared Chinese herbal (Shi-Bi-Lin) and placebo effects on percentage change from baseline scores for eight domains of SF-36. However, the effects between two groups were not compared.

iii. Medication consumption

Four trials counted rescue medication consumption during the trial (Hu 2002; Lenon 2012; Xue 2003a; Zhao 2009). Rescue medications were used by participants to relieve severe AR symptoms which could not be managed by the interventions during the trial period. The Hu 2002 study illustrated the use of rescue medication were reduced significantly in Biminne group compared to placebo for both immediate (MD 63.03; 95% CI 27.63 to 98.43) and long term follow-up (MD 39.41; 95% CI 17.27 to 61.55), respectively. The pooled data from the Xue 2003a and Lenon 2012 revealed no significant difference in relief medication scores in Chinese herbal and placebo groups during the treatment period (MD -3.13; 95% CI -7.10 to 0.84) (Figure 18). The Zhao 2009 trial indicated 13 patients in Shi-Bi-Lin group and 11 patients in placebo group took extra concurrent medication to control PAR symptoms but no scores were provided. Xue 2003a noted no significance difference detected between the active and the control, no data were available for further analysis.

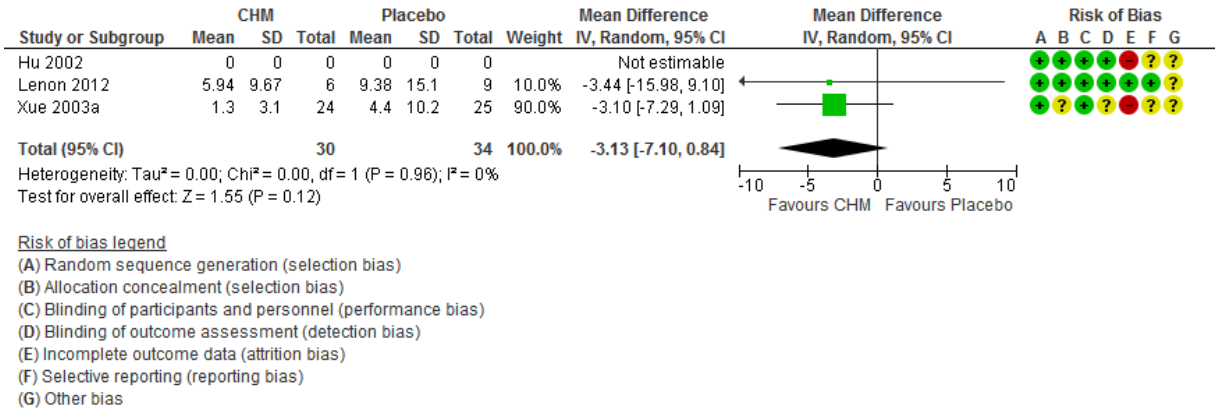


Figure 18. Medication consumption score for CHM versus placebo

iv. Total serum IgE level

Five studies assessed the total serum IgE level right after the treatment period (Hu 2002; Jung 2011; Matkovic 2010; Xue 2003a; Zhao 2009). However, the Hu 2002 trial only reported the median as well as lower and upper quartiles. All the Matkovic 2010, Xue 2003a and Zhao 2009 studies claimed that there were insignificant differences in changing IgE levels between two groups but no data were provided. Thus meta-analysis could not be performed. The Jung 2011 trial did not show significant difference in the total serum IgE level between ginseng and placebo at the end of four-week treatment (MD 16.39; 95% CI -11.41 to 44.19).

v. Adverse events

Almost all seven trials reported on adverse events. Baba 1995 trial reported six mild and one moderate case (digestive problems, headache, facial oedema, stomatitis, and belching) in treatment group, and five mild and two severe cases (eye dryness, thirst, and digestive problems) in control group. Both groups had one case presenting with a mild increase in aspartate aminotransferase (AST) and alanine transaminase (ALT). The Hu 2002 study had three cases (nausea, bloating, flatus, headache, sore eyes and sore nose) in treatment group and four cases (diarrhoea, vomiting, dizziness, rash on eyes, headache, vomiting, nose bleeding and spreading facial brown pigmentation) in control group. These mild to moderate adverse events were "considered to be possibly, probably or definitely related to study medication". However, no treatment was required for these adverse events. Two patients withdrew from the control group due to stomach upset and dull abdominal pain. The Jung 2011 trial reported one mild hepatic dysfunction (an increase in AST) in treatment group whilst in control group, a patient had an increase in total bilirubin and another patient had an increase in AST. The Lenon 2012 trial reported six cases (constipation, tiredness, itchiness around the mouth, dry nose at night and skin rash) in treatment group and 9 cases (nausea, tiredness, headache, dry nose at night, stomach upset and reflux) in control group. Ten participants in the Matkovic 2010 study reported 15 adverse events which included pharyngitis (seven), rhinosinusitis (four), enterocolitis (one), nausea (one), lacunar angina (one) and vulvitis (one); all signs were not connected to any intervention. However, no information on participants' grouping was available. Six patients from treatment group and five from control group experienced adverse events in the Xue 2003a trial. They experienced mild bloating, ingestion, stomach ache and/or dry nose which did not require any additional treatment. Only one patient in treatment group had severe skin rash and leg oedema which led to withdrawal from the trial. The Zhao 2009 trial reported 12 patients in treatment group and 10 in control group experienced abdominal

pain, diarrhoea, sore throat, skin itchiness and dry mouth. These adverse events were unrelated to the intervention used.

5.4.2. CHM versus Western medicine

A total of 37 studies compared CHM to Western medicine. Both Chen 2004 and Xie 2009 employed three-arm studies thus only CHM versus Western medicine component are included in this section.

A total of 27 trials assessed CHM against oral WM (Bao 2013, Cao 2007; Chen 2014; Gao 2009; Guo 2010; Han 2002; Hong 2005; Huang 2008a; Huang 2010; Jiang 1997; Jin 2010; Liang 2011b; Liu 2001; Lu 2011; Luo 2013; Peng 2001; Peng 2004; Qin 2006; Qiu 2012; Shen 2004; Sun 2014a; Yan 2011; Yang 2004; Ye 2015; Zhang 1996; Zhang 2007b; Zhong 2013). Zhang 1996 compared CHM oral to immunotherapy. Six trials compared CHM with WM nasal sprays only (Chen 2012; Huang 2006b; Wang 2000a; Zheng 2007; Zou 2012, Zhou 2001b). Only one (Wu 2009) used nano-liposome nasal drops for the control. Only one trial involved CHM oral plus external versus WM oral and nasal spray as comparators (Xin 2005) while two studies compared CHM with radiofrequency (Chen 2004; Xie 2009).

i. Improvement of symptoms

Seven non-classified AR studies evaluated global symptom improvement with immediate follow-up when comparing CHM with oral WM (Lu 2011; Shen 2004; Sun 2014a; Wang 2000a; Wu 2009; Zheng 2007; Zhou 2001b). Another eight studies for PAR fall under this category (Guo 2010; Huang 2008a; Liu 2001; Peng 2004; Qin 2006; Yan 2011; Zhang 2007b; Zou 2012). The overall pooled data demonstrated CHM had better significant effects over WM (RR 1.13; 95% CI 1.09 to 1.17) with substantial heterogeneity (I^2 = 75%). Subgroup analysis of global symptom improvement for immediate follow-up demonstrated CHM was more effective than WM group in treatment of non-classified AR (RR 1.21; 95% CI 1.14 to 1.28) as well as for PAR (RR 1.08; 95% CI 1.02 to 1.13). The heterogeneity for the latter is regarded as substantial (I^2 = 84%) and the former was moderate at (I^2 = 41%) (Figure 19).

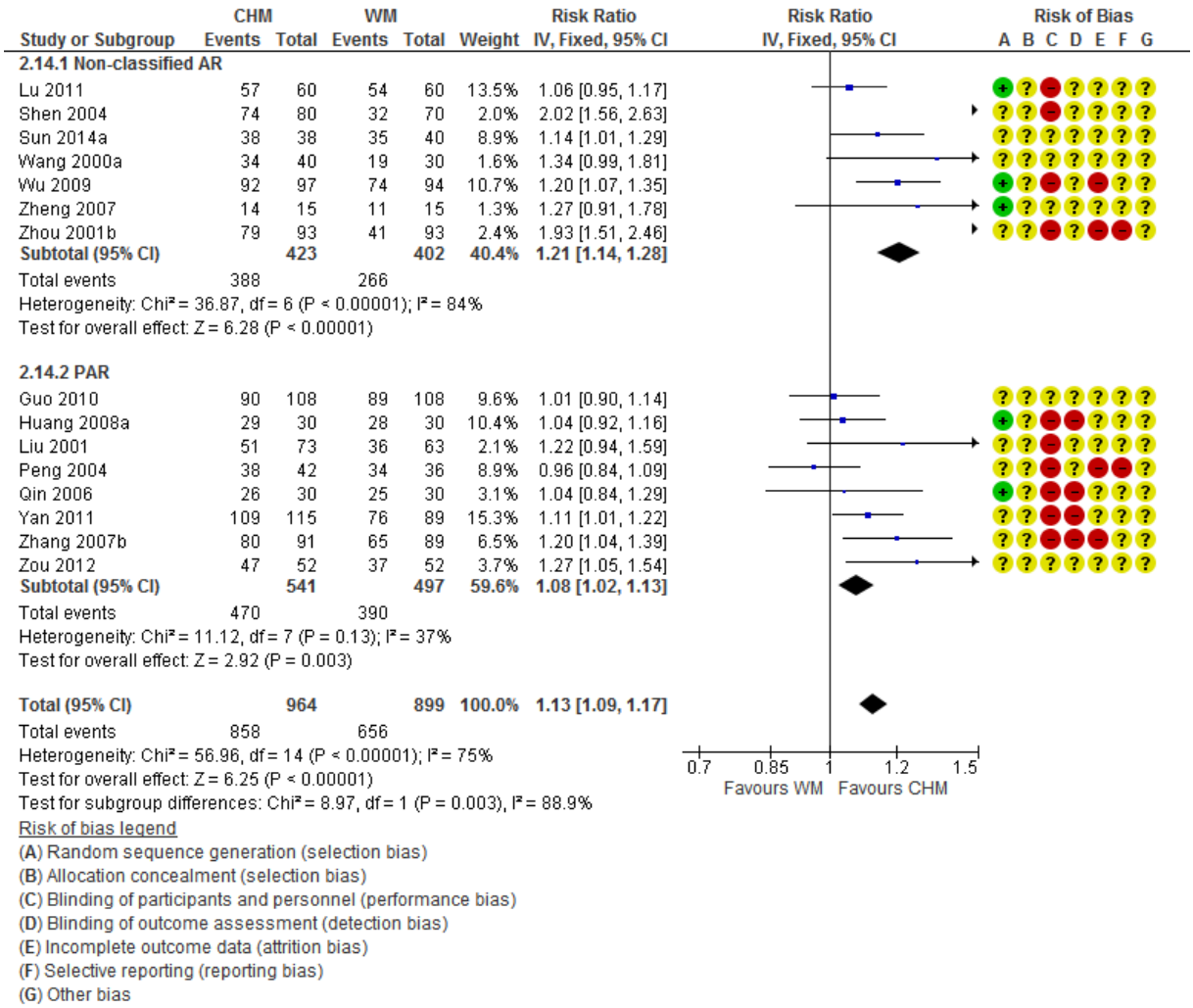


Figure 19. Global symptom improvement (immediate follow-up) for CHM versus WM

In short-term follow-up of AR treatment, ten studies for non-classified AR were also identified (Cao 2007; Chen 2012; Gao 2009; Guo 2010; Luo 2013; Peng 2001; Qiu 2012; Yang 2004; Ye 2015; Zheng 2007), while for PAR four studies were included (Liang 2011b; Xie 2009; Xin 2005; Zhang 1996). Effects of CHM in the short-term for non-classified AR was significant as reflected in the meta-analysis (RR 1.09; 95% CI 1.04 to 1.14) with low heterogeneity (I^2 = 7%). However, for PAR, CHM did not demonstrate clinical effects when compared to WM (RR 1.40; 95% CI 0.82 to 2.39) with substantial heterogeneity (I^2=83%). Overall, meta-analysis for short-term treatment in both groups showed CHM manifested positive symptom improvement in AR treatment (RR 1.12; 95% CI 1.04 to 1.21). However, heterogeneity is moderate (I^2 = 53%) (Figure 20).

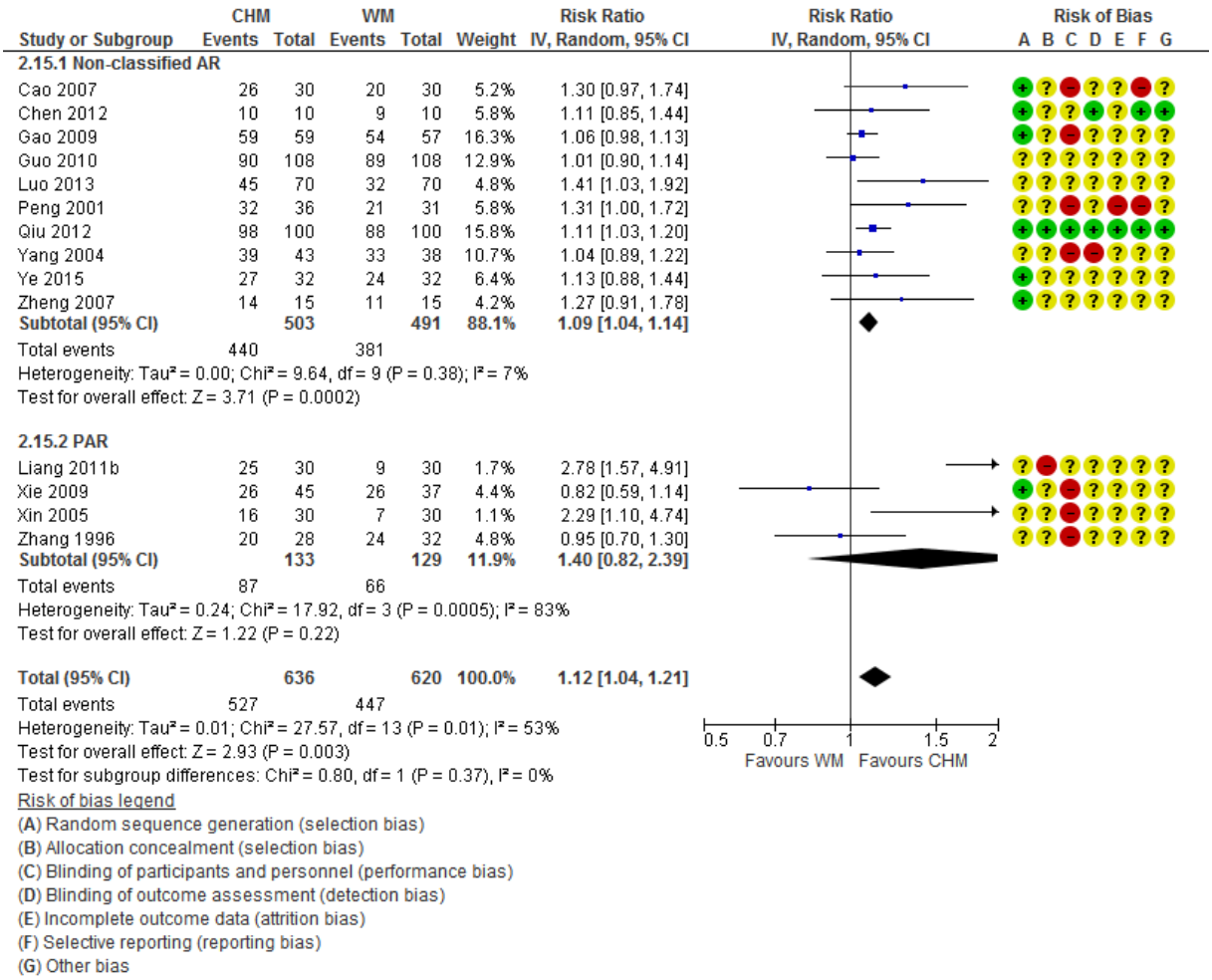


Figure 20. Global symptom improvement (short-term follow-up) for CHM versus WM

Four studies assessed global symptom improvement for intermediate follow-up (Hong 2005; Luo 2013; Huang 2010; Zhong 2013). Both Hong 2005 and Luo 2013 did not classify AR, while Huang 2010 and Zhong 2013 were PAR studies. Data for non-classified AR group showed a favourable global symptom improvement for patients using CHM (RR 1.24; 95% CI 1.10 to 1.39). No heterogeneity (I^2 = 0%) was detected. However, for PAR, no significant difference was shown (RR 1.44; 95% CI 0.75 to 2.74), with substantial heterogeneity (I^2 = 74%). Overall, meta-analysis demonstrated CHM had stronger clinical effects over WM for global symptom improvement (RR 1.21; 95% CI 1.08 to 1.37). Moderate heterogeneity was reflected (I^2 = 32%) (Figure 21).

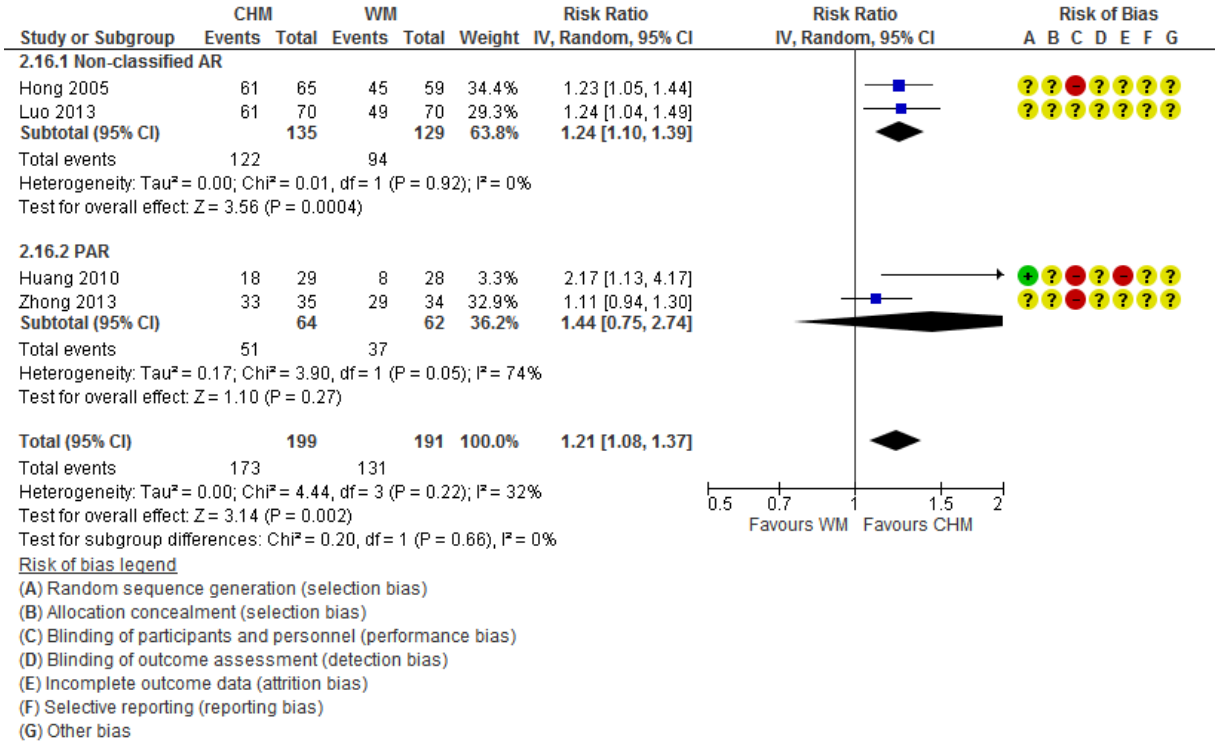


Figure 21. Global symptom improvement (intermediate follow-up) for CHM versus WM

Pooled data did not show any significant difference in global symptom improvement between CHM and WM for either PAR (RR 0.90; 95% CI 0.77 to 1.05) or non-classified AR (RR 1.13; 95% CI 0.95 to 1.33) over long-term follow-up in four studies (Han 2002; Chen 2004; Jin 2010; Liu 2001). However, heterogeneity was substantial for PAR studies (I^2 = 78%) (Figure 22).

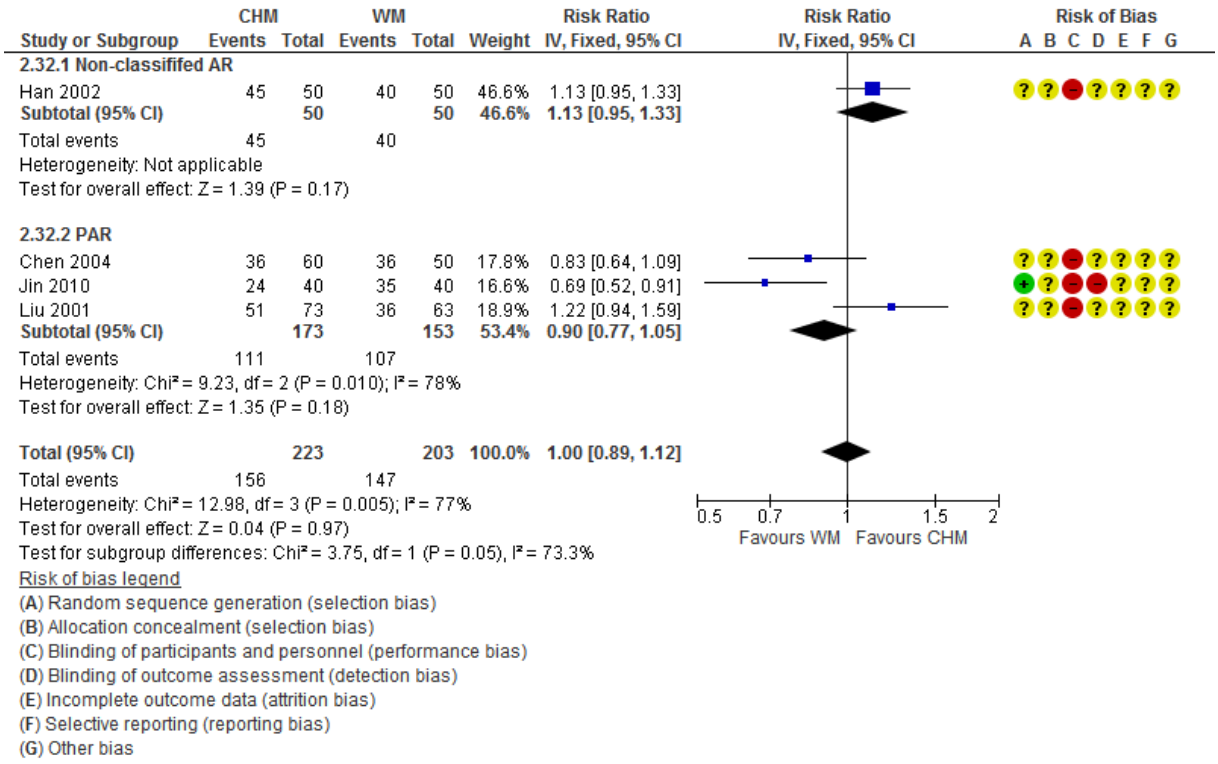


Figure 22. Global symptom improvement (long-term follow-up) for CHM versus WM

A further *post hoc* subgroup analysis conducted for global symptom improvement with the use of CHM versus anti-histamines for both non-classified AR and PAR indicated that CHM was more effective than anti-histamines for improving global symptoms improvement (RR 1.07; 95% CI 1.01 to 1.12) with immediate follow-up with heterogeneity at I^2 = 48% in the pooled data. However, results did not show significant difference for non-classified AR (RR 1.08; 95% CI 0.98 to 1.19) and PAR (RR 1.06; 95% CI 0.99 to 1.12) specifically. The heterogeneity for the non-classified AR and PAR studies only were substantial (I^2 = 71%) and low (I^2 = 28%), respectively (Figure 23).

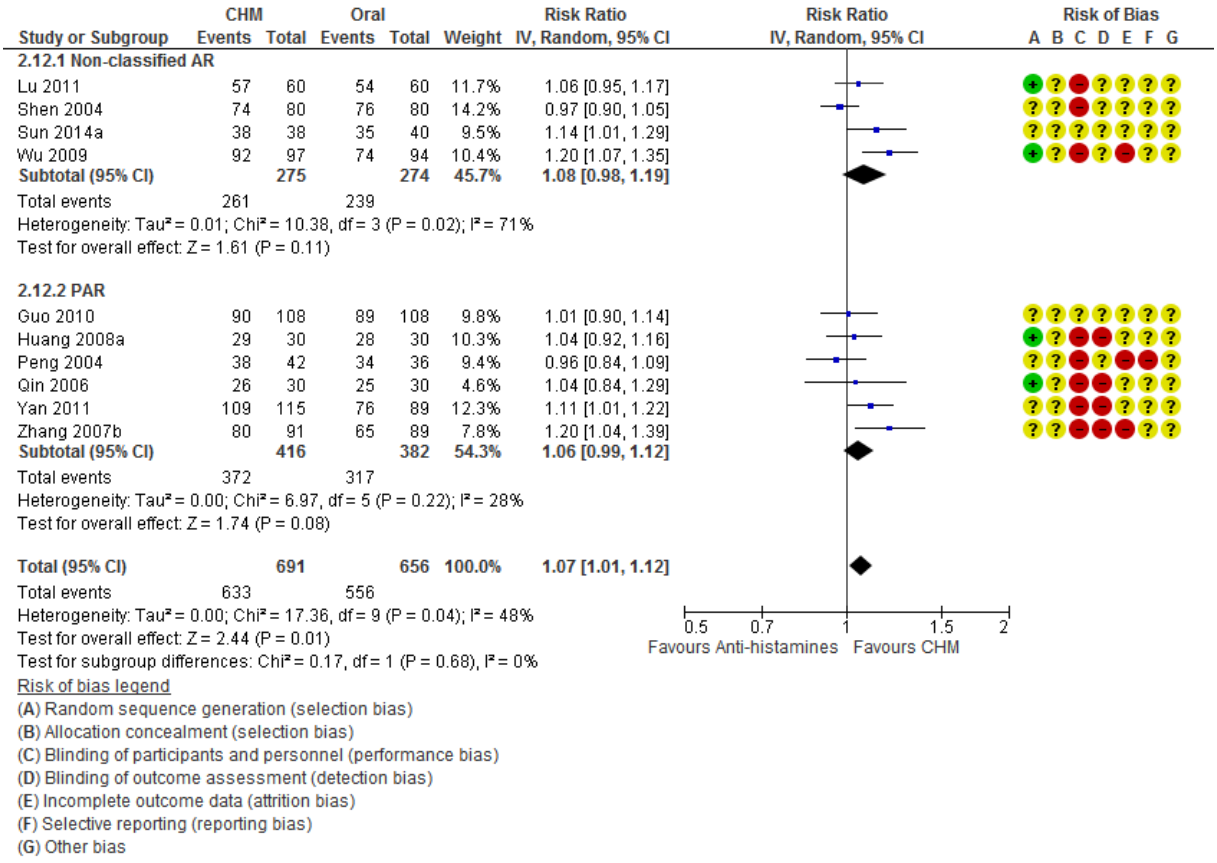


Figure 23. Global symptom improvement (immediate follow-up) *post hoc* analysis for CHM versus anti-histamines

Similar positive results prevailed for short-term follow-up for the use of CHM comparison to anti-histamines. For short-term follow-up, six non-classified AR studies (Cao 2007; Gao 2009; Luo 2013; Peng 2001; Yang 2004; Ye 2015), two PAR studies (Li 2012b; Liang 2011b) and one SAR study (Qiu 2012) were evaluated. Overall pooled data demonstrated CHM manifested significant difference over anti-histamines in global symptom over short-term (RR 1.19; 95% CI 1.07 to 1.33) with considerable heterogeneity (I^2 = 74%) (Figure 24).

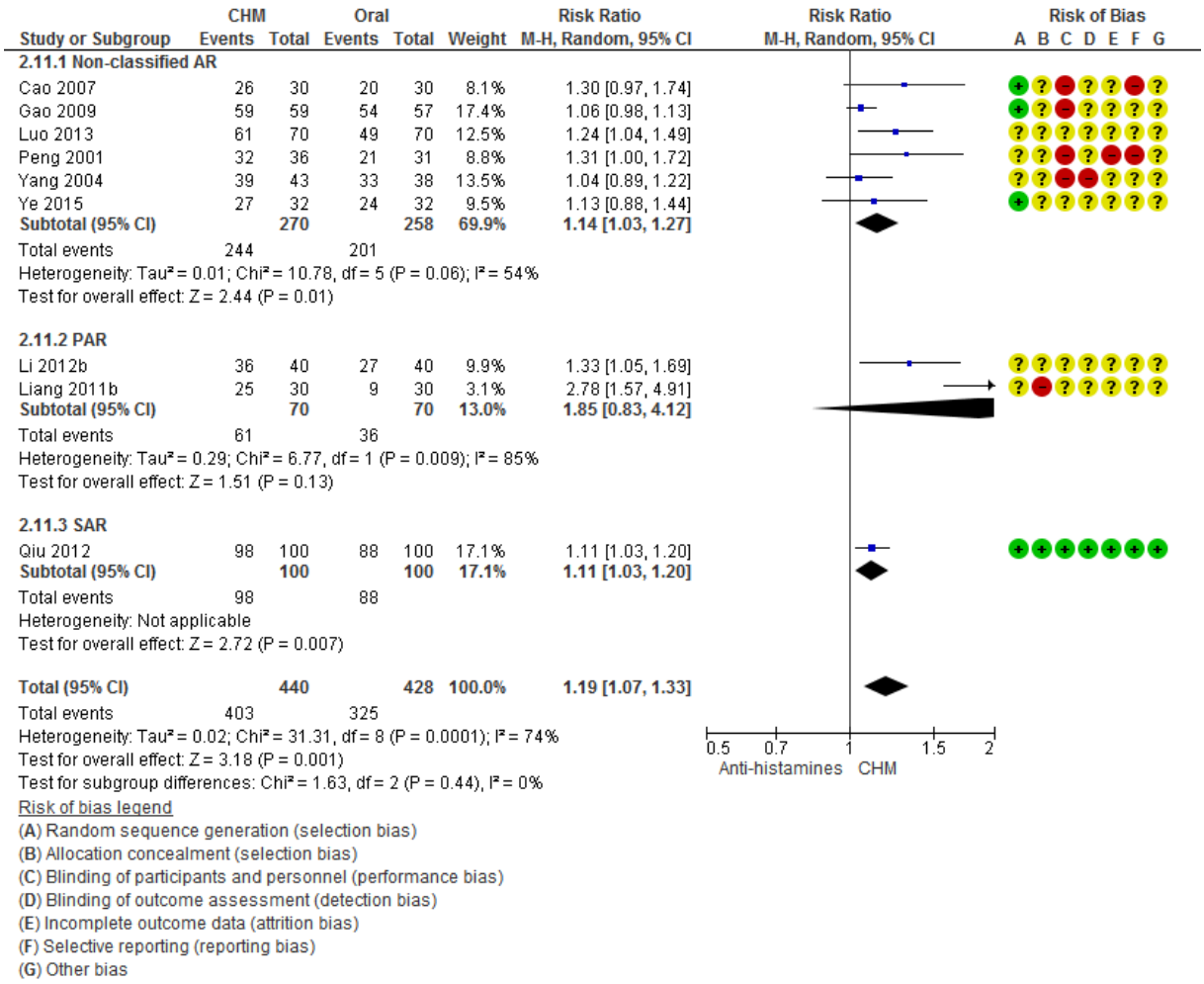


Figure 24. Global symptom improvement (short-term follow-up) *post hoc* analysis for CHM versus anti-histamines

Intermediate period evaluation of global symptom improvement involved two studies (Huang 2010 and Zhong 2013). There was no significant difference between CHM and WM (RR 1.52; 95% CI 0.58 to 3.99) (Figure 25).

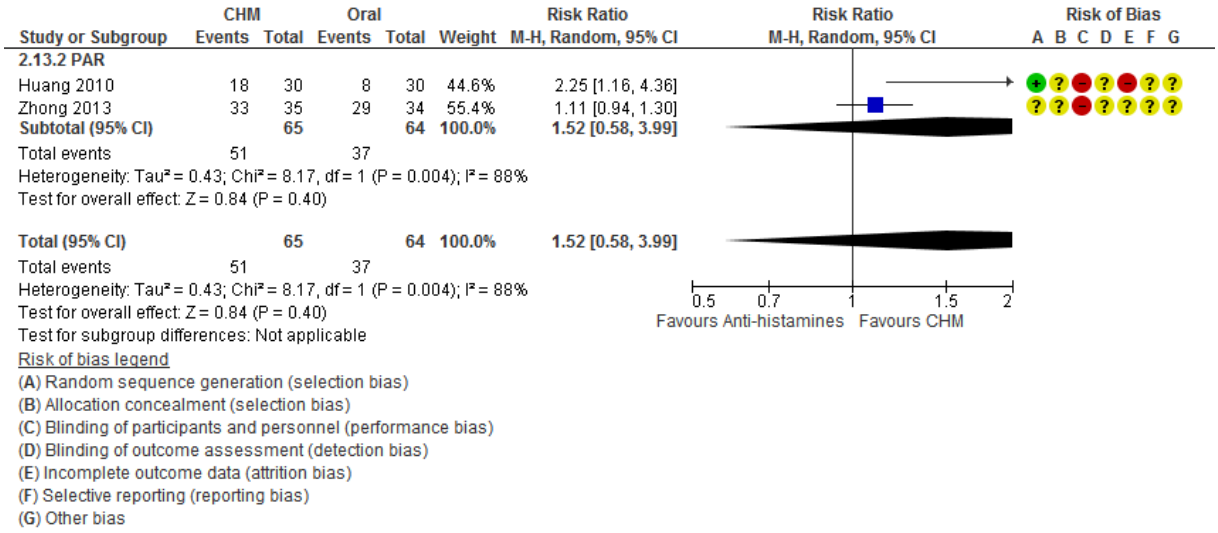


Figure 25. Global symptom improvement (intermediate follow-up) *post hoc* analysis for CHM versus anti-histamines

Summarily, meta-analysis results for global symptom improvement for CHM versus WM before *post hoc* analysis indicated for immediate (RR 1.13; 95% CI 1.09 to 1.13; I^2 = 75%), short-term (RR 1.12; 95% CI 1.04 to 1.21; I^2 = 53%), intermediate (RR 1.21; 95% CI 1.08 to 1.37; I^2 = 32%) and long-term effects (RR 1.00; 95% CI 0.89 to 1.12; I^2 = 77%), respectively. Global improvement for AR symptoms was significant with immediate, short-term and intermediate effects but not in the long-term. The *post hoc* analysis indicated for CHM versus anti-histamines over immediate (RR 1.07; 95% CI 1.01 to 1.12; I^2 = 48%), short-term (RR 1.21; 95% CI 1.07 to 1.37; I^2 = 78%) and intermediate effects (RR 1.52; 95% CI 0.58 to 3.99; I^2 = 88%). CHMs were superior over anti-histamines in immediate and short-term duration.

As different WMs were used in the control group, subgroup analyses were performed according to WM. Subgroup analyses for all the oral western medications involved in the control groups that involve anti-histamines included Cetirizine (Huang 2010; Jiang 1997; Liu 2001; Lu 2011;

Qin 2006; Shen 2004; Yan 2011); Loratadine (Bao 2013; Gao 2009; Guo 2010; Liang 011; Luo 2013; Peng 2004; Qiu 2012; Sun 2014a; Ye 2015; Zhang 2007b; Zhong 2013), Ketotifen (Cao 2007; Peng 2001), Hismanal (Jiang 1997; Han 2002) and Triprolidine (Qin 2006; Yang 2004).

In Figure 26, Subgroup 2 consists of CHM external (*Magnolia Fl*os volatile oil nano-liposome nasal drops) versus WM oral medication in one study (Wu 2009). Subgroup 3, CHM external versus WM external (nasal spray) were used (Wang 2000a; Zhou 2001b). Only Zou 2012 in Subgroup 4 used CHM oral versus WM external (nasal spray).

The use of *Magnolia Fl*os volatile oil nano-liposome nasal drops in Wu 2009 in Subgroup 2 exhibited significant difference over Cetrizine (RR 1.24; 95% CI 1.11 to 1.39) (Figure 26, 2.5.2) after the last treatment. The use of CHM external in comparison with WM external in Subgroup 3 exhibited effects at the end of treatment period (RR 1.63; 95% CI 1.14 to 2.32) (Figure 26, 2.5.3).

In Subgroup 4, oral administration of Tuomintongqiao capsule (includes six CHMs) was more effective than external application of Montelukast nasal drops (RR 1.27; 95% CI 1.05 to 1.54) (Figure 26, 2.5.4) in Zou 2012. Overall, meta-analysis of global symptom improvement for immediate follow-up demonstrated CHMs had a significant impact in treatment of AR. (RR 1.12; 95% CI 1.05 to 1.20). Heterogeneity is substantial (I^2 = 71%) (Figure 26).

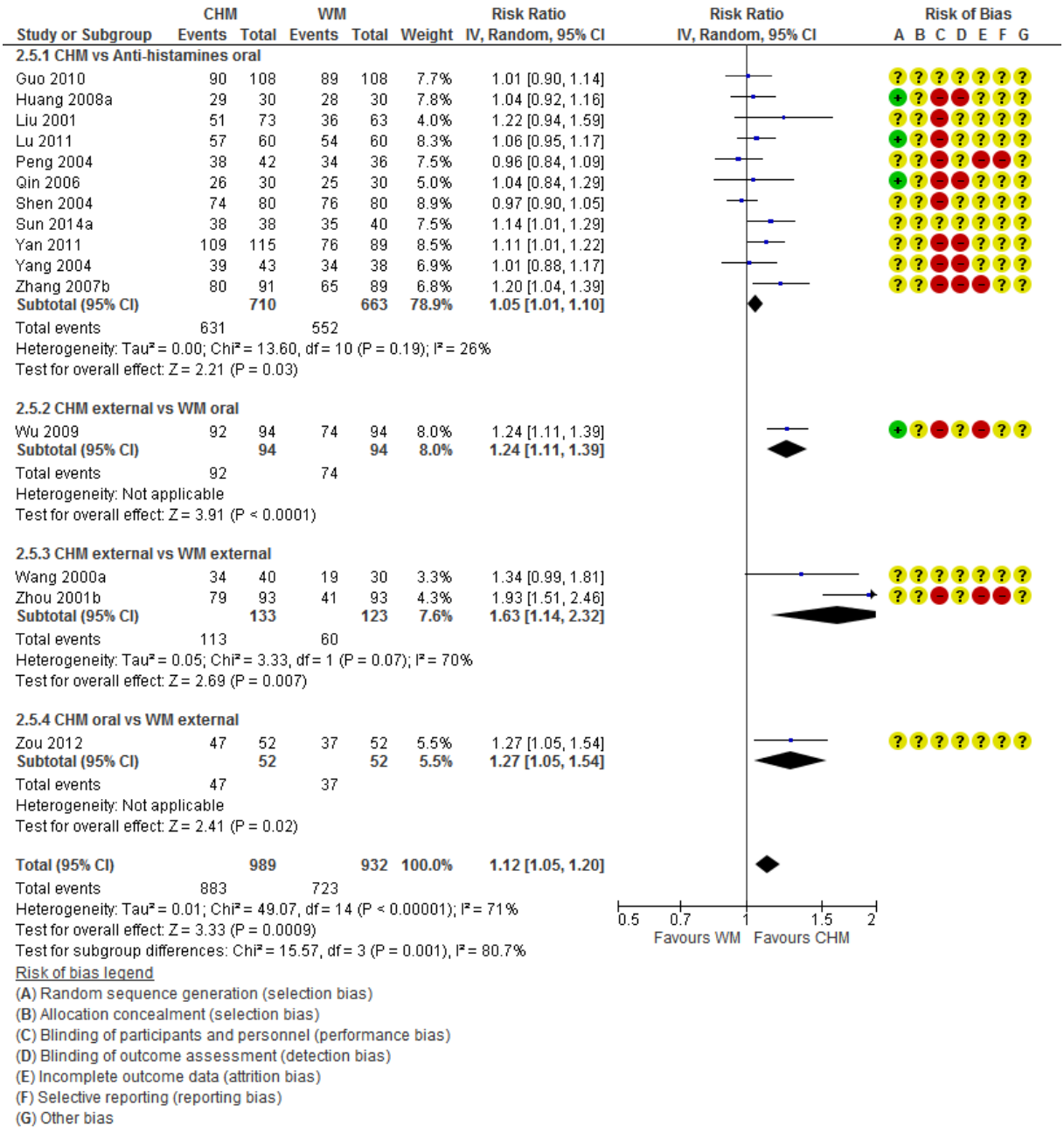


Figure 26. Global symptom improvement (immediate follow-up) with subgroup analysis for CHM versus WM

In the subgroup analysis, global symptom improvement (short-term follow-up) demonstrated favourable effects of CHM over WM (RR 1.13; 95% CI 1.03 to 1.24). Substantial heterogeneity is at (I^2 = 65%). No significant difference was depicted for CHM when taken in different forms such as external versus WM external (RR 1.17; 95% CI 0.95 to 1.44), immunotherapy (RR 0.95; 95% CI 0.70 to 1.30) and radiofrequency (RR 0.82; 95% CI 0.59 to 1.14) for improving global symptom over the short-term period. However, CHM exhibited more effectiveness over

the use of oral anti-histamines (RR 1.15; 95% CI 1.03 to 1.28) with a substantial heterogeneity (I^2 = 73%) (Figure 27).

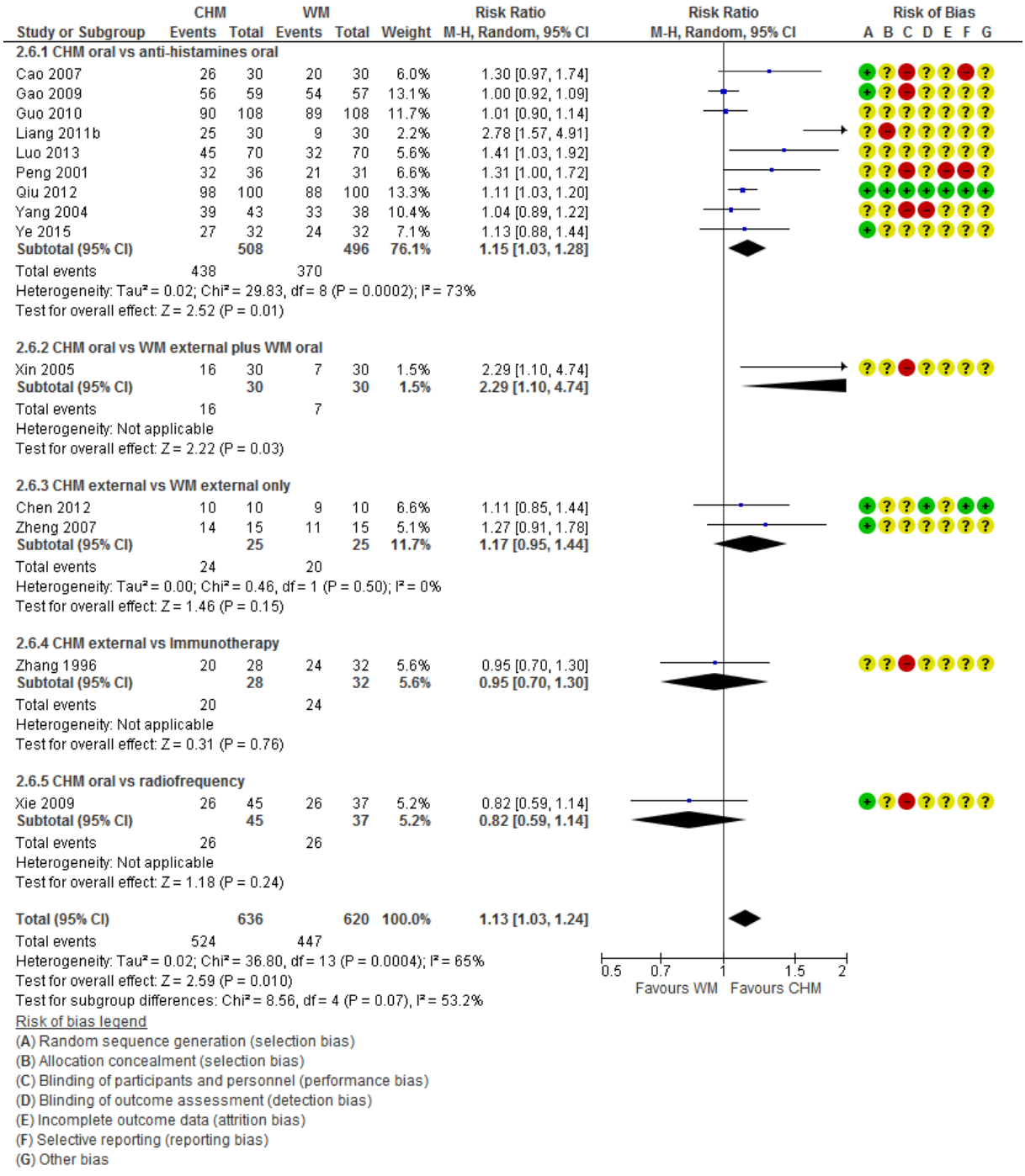


Figure 27. Global symptom improvement (short-term follow-up) with subgroup analysis for CHM versus WM

Contradictory outcome is portrayed in the data for intermediate evaluation of global symptom improvement. CHM was significant as manifested in study of Hong 2005 (RR 1.23; 95% CI

1.05 to 1.44) for CHM oral in comparison with WM oral and WM external, but not for anti-histamine use in Huang 2010, Luo 2013 and Zhong 2013 (RR 1.27; 95% CI 0.98 to 1.63). However, pooled data analysis depicted CHM had more significant effects in improving global symptom when compared to WM in the intermediate period (RR 1.23; 95% CI 1.06 to 1.42) with moderate heterogeneity (I^2 = 50%) (Figure 28).

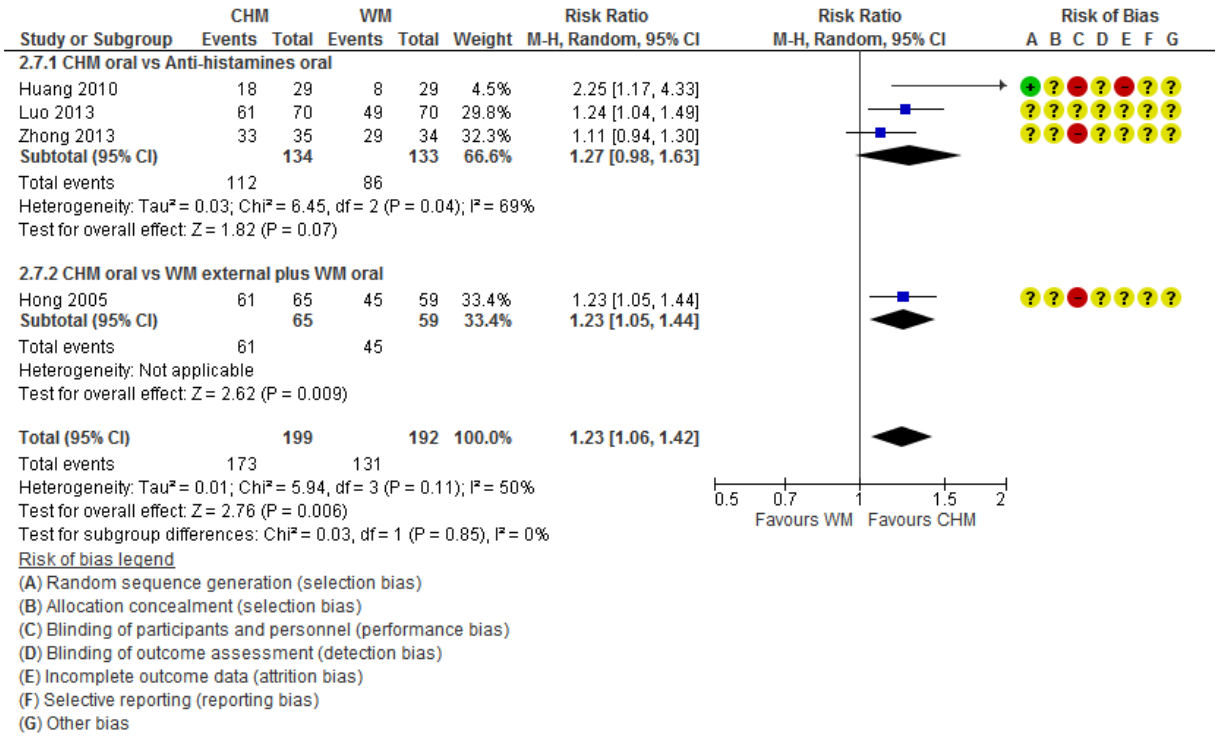


Figure 28. Global symptom improvement (intermediate follow-up) with subgroup analysis for CHM versus WM

Pooled data for global symptom improvement over long-term follow-up demonstrated no significant difference (RR 0.95; 95% CI 0.74 to 1.22) with substantial heterogeneity (I^2 = 77%) (Figure 29).

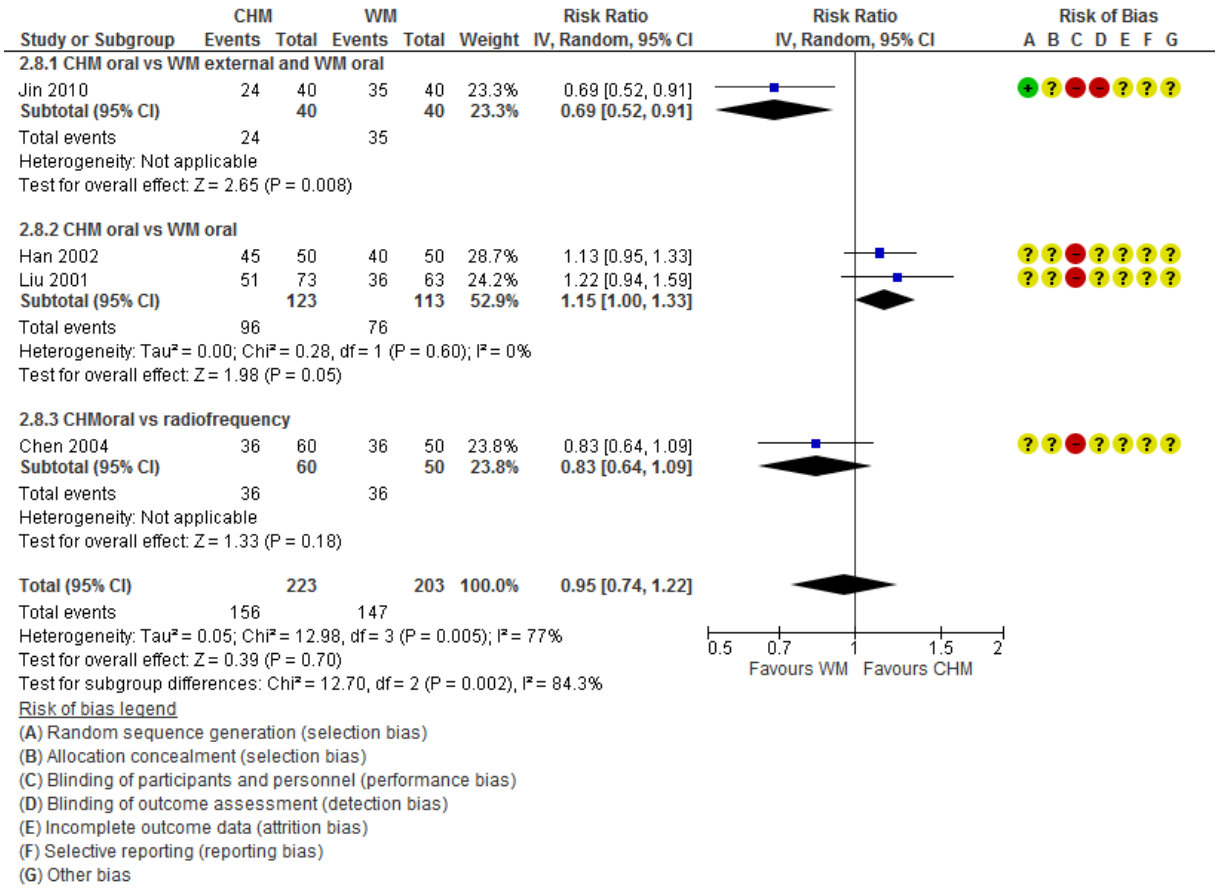


Figure 29. Global symptom improvement (long-term follow-up) with subgroup analysis for CHM versus WM

For severity of symptoms, three trials compared the severity of the different AR symptoms at the end of the treatment period using mean value with SD (Lu 2011; Peng 2004; Wu 2009). In comparison with WM, the pooled data indicated that CHM had no significant effects on sneeze (SMD -0.51; 95% CI -1.20 to 0.17) (Figure 30), runny nose (SMD -0.47; 95% CI -1.05 to 0.10) (Figure 31) and nasal congestion (SMD -0.44; 95% CI -1.11 to 0.23) (Figure 32). Only severity for itchy nose score demonstrated positive results with a favour to CHM (SMD -0.28; 95% CI -0.48 to -0.07) (Figure 33). The heterogeneity for sneeze, runny nose and nasal congestion was considerable except for itchy nose score, I^2 = 90%, I^2 = 86% and I^2 = 89%, respectively. No heterogeneity was applicable for itchy nose I^2 = 0% (Figure 33).

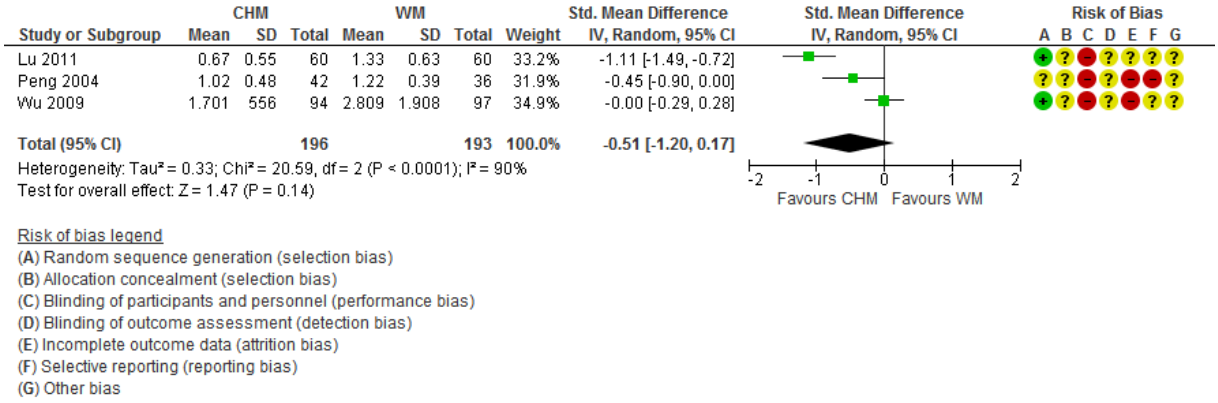


Figure 30. Severity of sneeze score (immediate follow-up) for CHM versus WM

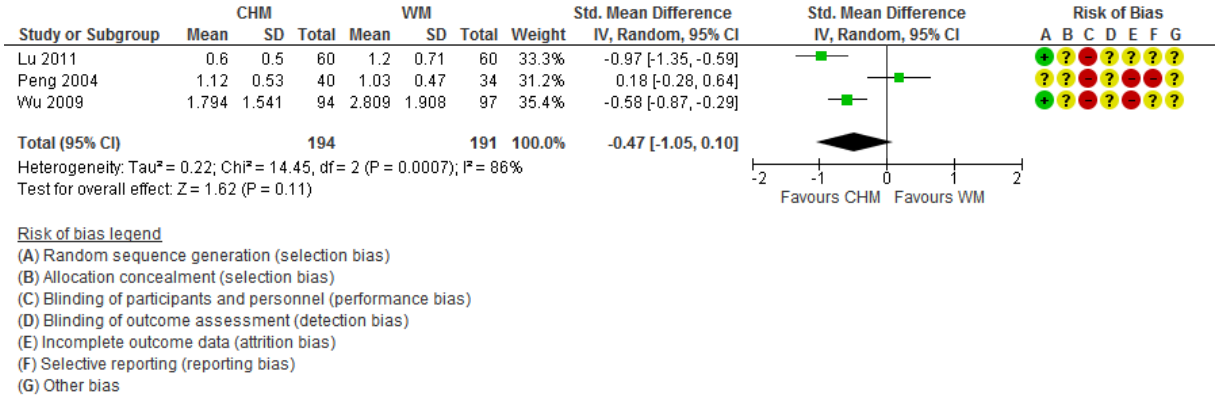


Figure 31.Severity of runny nose (immediate follow-up) for CHM versus WM

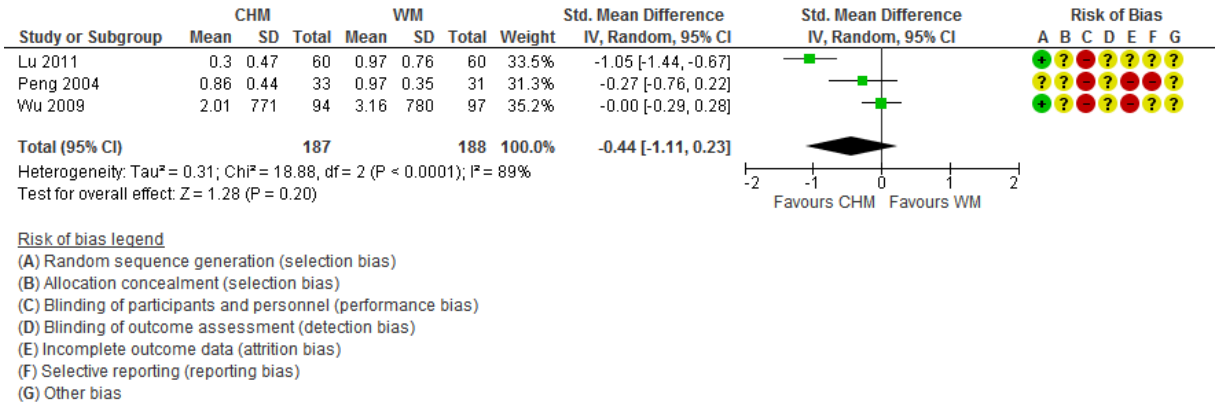


Figure 32. Severity of nasal congestion (immediate follow-up) for CHM versus WM

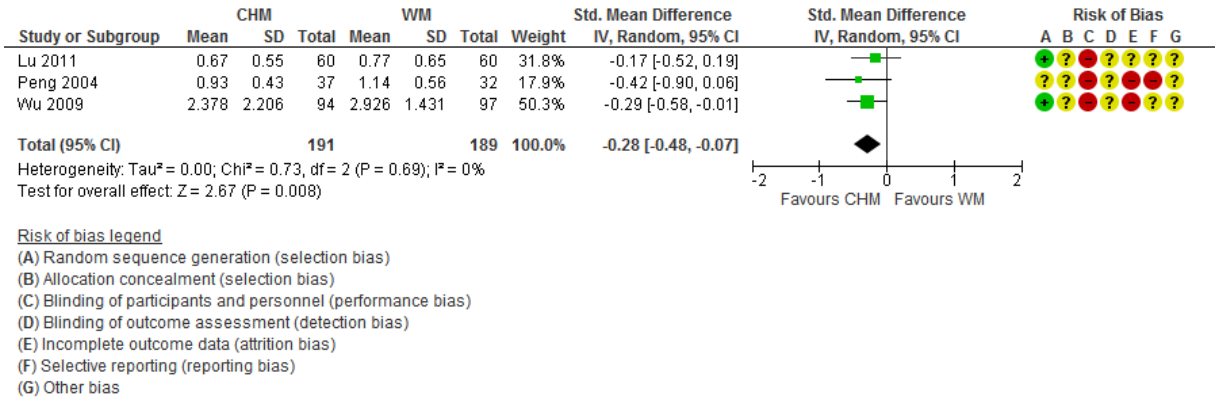


Figure 33. Severity of itchy nose (immediate follow-up) for CHM versus WM

Only Cao 2007 assessed patients' severity of symptom score in short-term follow-up, while Zhong 2013 evaluated severity in the intermediate period. Results showed that in the short term, CHM had less effects when compared to oral Ketotifen in Cao 2007 with sneeze (MD 0.73; 95% CI 0.21 to 1.26), runny nose (MD 1.17; 95% CI 0.62 to 1.72), nasal congestion (MD 0.74; 0.22 to 1.27) and itchy nose (MD 0.62; 95% CI 0.10 to 1.14). Positive trend is depicted in the data of Zhong 2013 when severity of symptoms was evaluated on Qufengtongqiao formula for PAR after intermediate duration of treatment. A positive effect was demonstrated in CHM for the severity of AR symptoms when compared to Desloratadine for a period of six months: sneeze (MD -0.60; 95% CI -1.08 to -0.11), nasal congestion (MD -0.83; 95% CI -1.33 to -0.34), itchy nose (MD -0.68; 95% CI -1.17 to -0.19) and runny nose (MD -0.91; 95% CI -1.40 to -0.41).

Four studies assessed global symptom score at the end of treatment period (Bao 2013; Huang 2006b; Peng 2004; Zou 2012). There was no significant difference in global symptom score between CHM and WM oral groups (SMD -0.87; 95% CI -1.79 to 0.05) right after the treatment period. Considerable heterogeneity was reflected (I^2 = 90%) (Figure 34). The same trend is also observed in short-term assessment of global symptoms except for Qiu 2012 where syndrome differentiation was employed in the trial (Figure 35). Positive global symptom outcome was

depicted in CHM group compared to WM in Qiu 2012 (SMD -2.87; 95% CI -3.27 to -2.48). Insignificant difference for non-classified AR was observed in the meta-analysis for Cao 2007; Gao 2009 and Peng 2001 (SMD 0.11; 95% CI -0.74 to 0.96). Overall pooled data demonstrated no effect was exerted by CHM following a short-term period (SMD -0.63; 95% CI -2.22 to 0.95). A high heterogeneity is depicted (I^2 = 98%) (Figure 35).

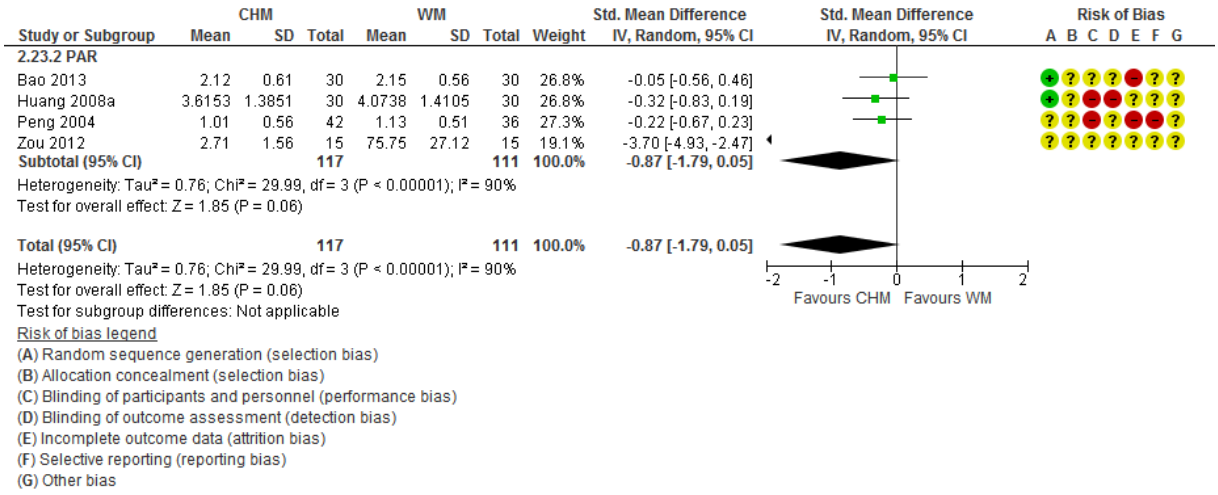


Figure 34. Global symptom score (immediate follow-up) for CHM versus WM

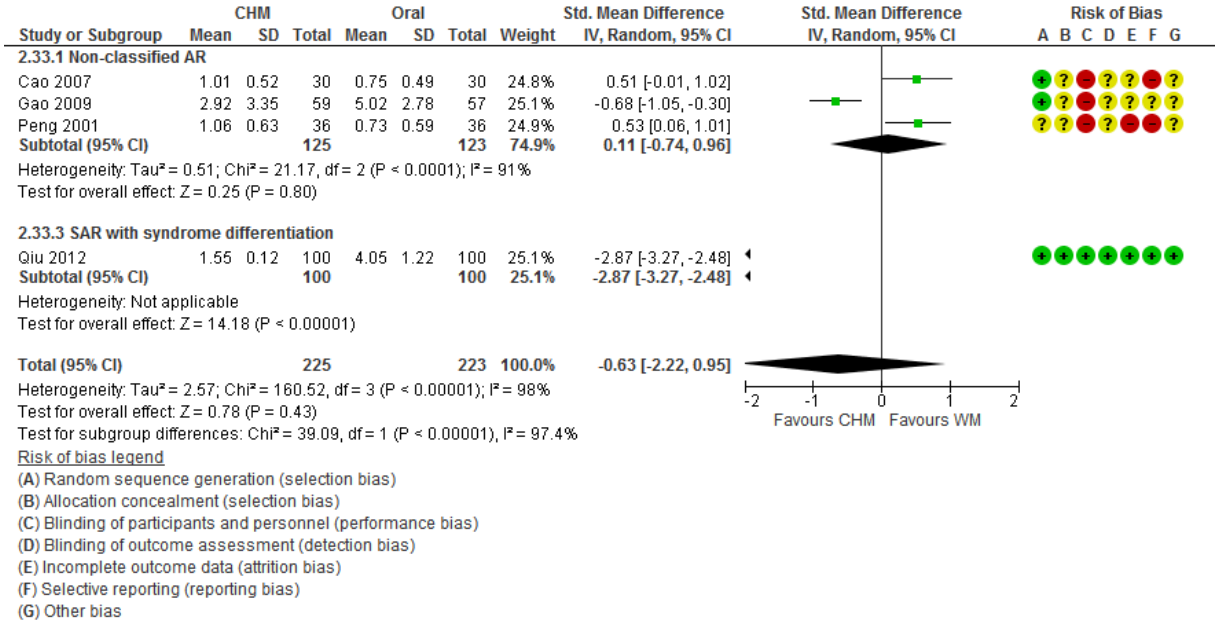


Figure 35. Global symptom score (short-term follow-up) for CHM versus WM

Both Huang 2010 and Zhong 2013 assessed total symptom score for CHM versus WM for PAR in the intermediate period (six months after treatment). It appeared that CHM did not exert

significant difference in the symptom score associated with PAR subgroup when compared to WM oral (SMD -0.33; 95% CI -1.88 to 1.22). Substantial heterogeneity exists (I^2 = 94%) (Figure 36).

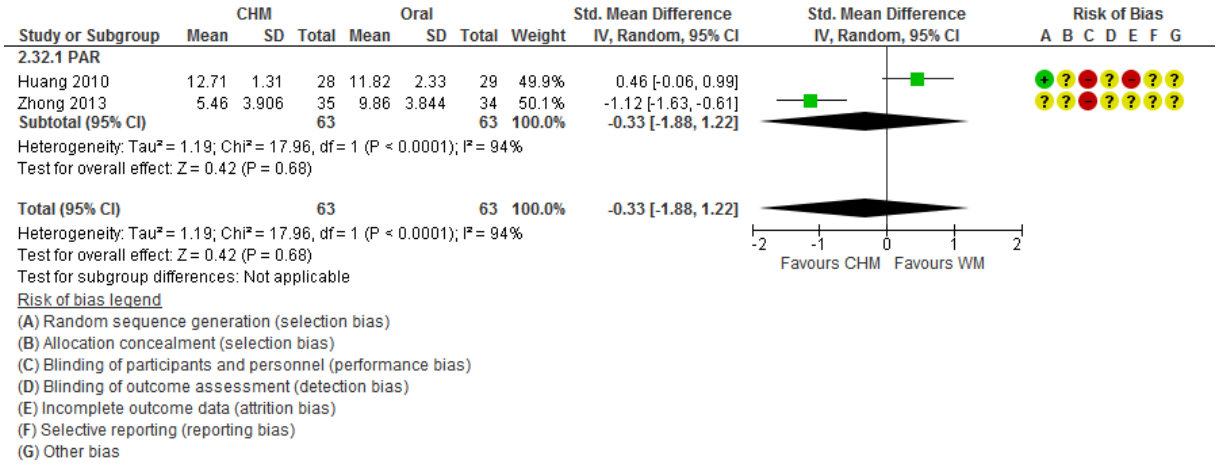


Figure 36. Global symptoms score (intermediate follow-up) for CHM versus WM

No studies reported data on total symptom scores for long-term follow-up.

ii. Quality of life

Only one trial Gao 2009 assessed the effects on quality of life using SF-36. The scores in the eight domains of SF-36 and Chinese herbs (Lingguizhugan decoction) showed more improvement than Loratadine tablet for PAR patients with phlegm retention at the end of two weeks' treatment. The following three domains: physical functioning (MD 2.77; 95% CI 0.49 to 5.05), role limitations due to physical health problems (MD 6.82; 95% CI 0.90 to 12.74) and general health (MD 6.25; 95% CI 0.28 to 12.22) were significant. There were no significant differences between two groups in the other five domains which included, bodily pain (MD 2.81; 95% CI -2.09 to 7.71), vitality (MD 1.04; 95% CI -5.32 to 7.40), social functioning (MD 4.38; 95% CI -0.30 to 9.06), role limitations due to emotional problems (MD 8.42; 95% CI -2.96 to 19.80) and mental health (MD 1.89; 95% CI -4.10 to 7.88).

iii. Medication consumption

None of these 37 studies recorded the use of rescue medication.

iv. Total serum IgE level

The total serum IgE level was evaluated in four trials (Chen 2012; Han 2002; Zhang 1996; Zhou 2001b). However, the Han 2002 study reported the Chinese herbs could reduce serum IgE level (iu/ml) significantly in a long-term (one year after treatment period) with comparison to Hismanal tablet (MD -64.50; 95% CI -69.64 to -59.36). Both Chen 2012 and Zhang 1996 reported no significant difference between CHM and WM in the IgE levels for the immediate follow-up (MD -401.96; 95% CI -982.59 to 178.67) and short-term follow-up (MD 18.20; 95% CI -48.97 to 85.37) (Figure 37).

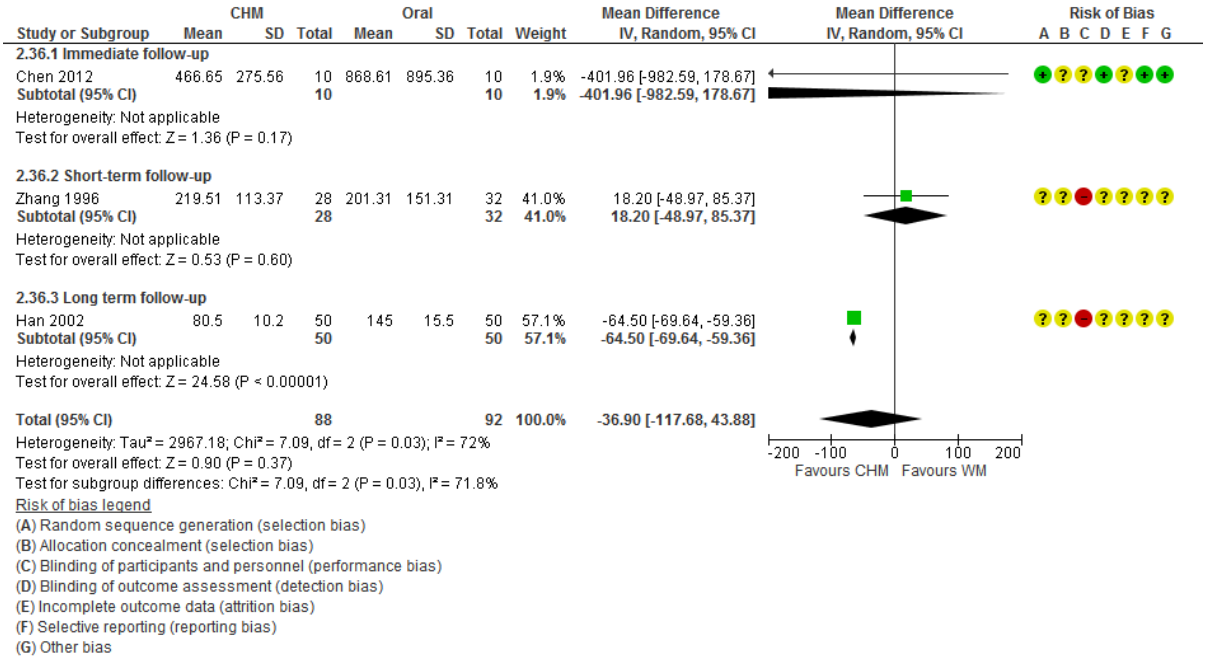


Figure 37. Total serum IgE levels assessed over different follow-up periods for CHM versus Western medicine

v. Adverse events

Twenty included studies reported information on adverse events and the rest of the studies did not report any.

The meta-analysis was performed for the nine studies with data in both groups (Gao 2009; Guo 2010; Han 2002; Hong 2005; Huang 2010; Peng 2004; Shen 2004; Wang 2000a; Zhou 2001b) using the ITT method. The *post hoc* subgroup analysis showed that CHM groups had less minor adverse events than WM groups (RR 0.20; 95% CI 0.08 to 0.49); however, there was no significant difference in major adverse events between two groups (RR 0.31; 95% CI 0.05 to 1.92) (Figure 38).

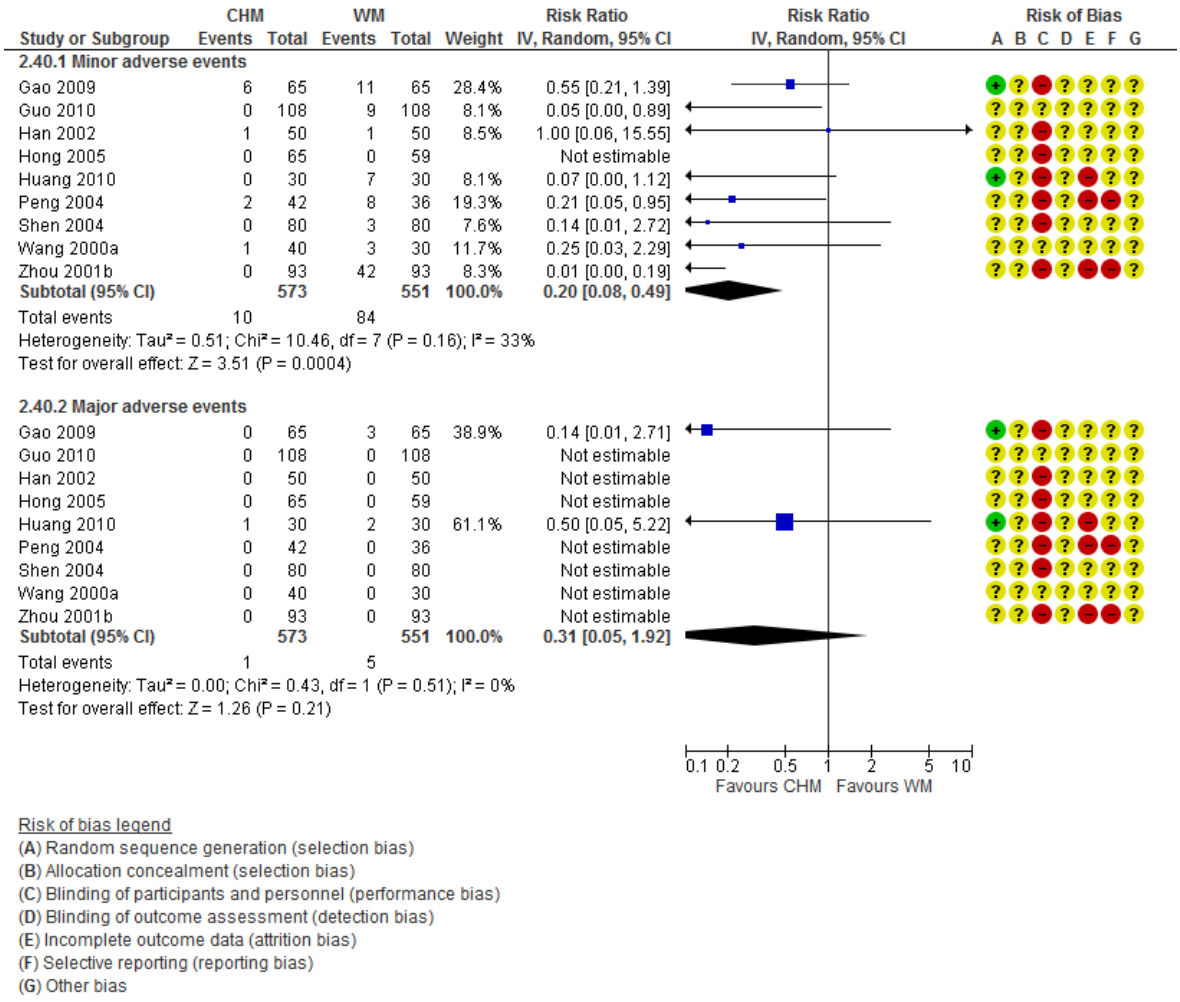


Figure 38. Adverse events with *post hoc* analysis for CHM versus WM

Common adverse events in control groups were lassitude, somnolence (sleepiness), dry mouth and dry nose. Three cases in Gao 2009 study experienced lassitude and somnolence which related to the use of Loratadine tablet. The Guo 2010 trial reported nine adverse events in control group including five cases with somnolence, one with headache, two with dry mouth

and one with nausea. The Huang 2010 study found seven cases including four with dry mouth, somnolence and lassitude, two with headache and dizziness, and one gastrointestinal discomfort. No additional treatment was provided to these adverse events. Three cases (one case with somnolence and two cases with dry mouth and dry nose) were reported in the Shen 2004 study. The Zhou 2001b trial found 31 cases with dry nose and 11 patients having high blood pressure with an increase of heartbeat and blood pressure. The Huang 2008a study observed rare adverse events in treatment group and some somnolence, lassitude and dry mouth in control group. However, no detailed data were provided. The Wu 2009 trial reported pain in nasal cavity; however, no detailed information was given.

Four trials reported adverse events in both groups (Han 2002; Peng 2004; Wang 2000a; Bao 2013). Han 2002 study observed one with stomach ache in treatment group and one with diarrhoea in control group. The Peng 2004 trial reported two patients in treatment group had dry mouth and dry nose (one case with blood in nasal discharge). Eight patients in control group experienced adverse events including five with lassitude and somnolence, two with nausea and vomiting, and one with mild skin itchiness. The Wang 2000a study found one adverse event (pain in nose) in treatment group whilst three (distending headache) in control group. No additional treatment was provided in these trials. Bao 2013 reported dry mouth, somnolence, and heart palpitation in both groups; however, no detailed data was provided. The rest of of the four trials reported no adverse events were associated with the therapeutic course.

In the three-arm studies (Zhang 1996, Chen 2004 and Xie 2009), both Zhang 1996 and Xie 2009 did not report any adverse event in their evaluation, only Chen 2004 cited no side effects were observed during the therapeutic course.

5.4.3. CHM plus co-intervention versus placebo plus same co-intervention

Only one study (Xue 2003b) employed the use of acupuncture as co-intervention to two groups.

i. Improvement of symptoms

Severity of nasal symptoms was assessed by patients and specialist for the treatment of SAR in this study. In terms of severity of nasal symptom, the data demonstrated CHM combined with acupuncture had no significant difference over placebo and acupuncture when assessed by both patient (MD 0.08; 95% CI -0.42 to 0.58) and specialist (MD 0.12; 95% CI -0.39 to 0.62) at the end of the treatment period. Similarly for non-nasal symptoms when assessed by patients (MD -0.08; 95% CI -0.58 to 0.42) and specialist (MD 0.02; 95% CI -0.49 to 0.52) alike, CHM did not exert additional effects in comparison to placebo when it is employed with acupuncture as co-intervention.

ii. Quality of life

With co-intervention (acupuncture), Xue 2003b did not find any significant difference in RQLQ Section One or Section Two scores between two groups (Section One: MD 0.15; 95% CI -0.36 to 0.65; Section Two: MD -0.35; 95% CI: -0.85 to 0.15).

iii. Medication consumption

The data from the Xue 2003b study reported that it did not observe any significant difference in relief medication scores in both groups during the treatment period. No detailed data were provided.

iv. Total serum IgE level

No IgE level was measured in this study.

v. Adverse events

The Xue 2003b study reported that three patients from the treatment and control group experienced mild gastrointestinal discomfort (bloating, indigestion and stomach ache) and bruising from acupuncture. No additional management was required for these minor adverse events.

5.4.4. CHM plus co-intervention versus same co-intervention only

A total of 17 trials were evaluated for the effects of CHM with co-intervention versus the same co-intervention only (Cao 2014b; Chen 2011; Li 2008; Li 2012b; Li 2012c; Lin 2013; Liu 2004b; Lu 1998; Lu 2003; Lu 2009; Shi 2012; Shi 2014; Tang 2008; Wu 2012a; Xiao 2015; Zhao 2012; Zhou 2005). Xiao 2015 conducted a four-arm trial of which two of the comparisons, CHM with WM (oral and external) versus same WM only; CHM with acupuncture and WM (oral and external) versus same acupuncture and WM only. The rest studies compared CHM plus Western medicine with the same Western medicine only.

Another three included studies (Chen 2004; Xie 2009; Zhang 1996) are three-arm trials. One of their comparisons, that is, CHM plus immunotherapy compared with same immunotherapy alone in Zhang 1996, CHM plus radiofrequency versus same radiofrequency alone in Chen 2004 and Xie 2009, were also included in this category.

In terms of the co-interventions, seven studies used both oral and external applications of WM in the control group (Li 2008; Li 2012b; Li 2012c; Lin 2013; Lu 2003; Lu 1998; Shi 2012). When used externally in the nasal cavity, one study compared Chinese herbal drops plus surgery with same surgery alone (Liu 2004b).

i. Improvement of symptoms

Global symptom improvement for immediate follow-up was assessed in nine trials namely, Cao 2014b; Chen 2011; Chen 2014; Li 2008; Li 2012c; Liu 2004b; Shi 2014; Tang 2008 and Zhao 2012. Meta-analysis demonstrated CHM plus co-intervention displayed a favourable tendency with a significant difference over the same co-intervention only (RR 1.26, 95% CI 1.05 to 1.51). However, substantial heterogeneity existed (I^2 = 82%) (Figure 39).

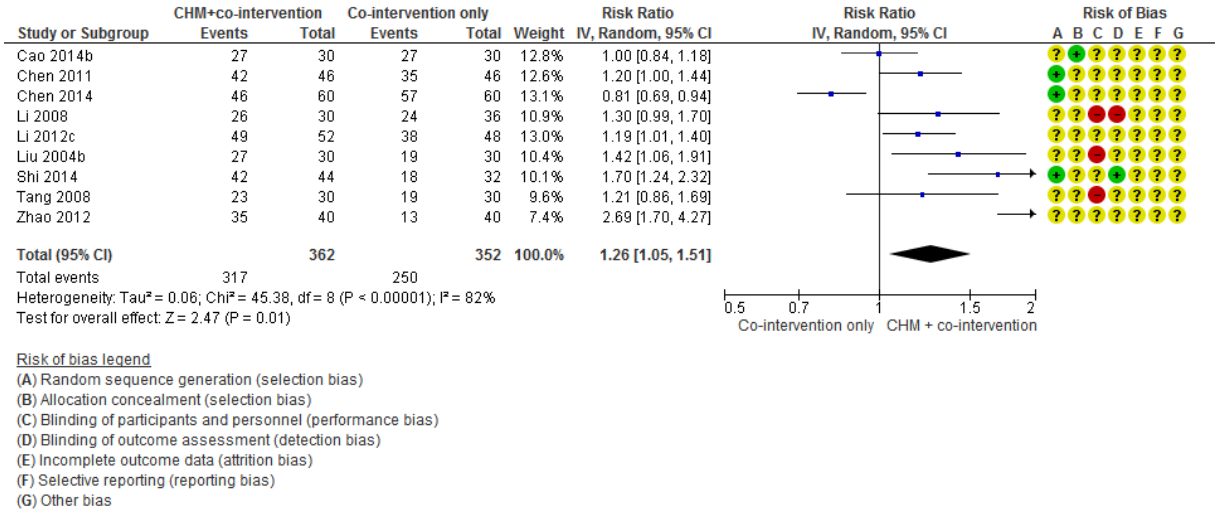


Figure 39. Global symptom improvement (immediate follow-up) for CHM plus co-intervention versus same co-intervention only

Four trials (Li 2012b; Lin 2013; Wu 2012a; Xie 2009) assessed global symptom improvement over a short-term period. Significant effects of CHM with co-intervention over same co-intervention when used alone were strongly featured (RR 1.27; 95% CI 1.15 to 1.39). No heterogeneity was depicted in the meta-analysis (I^2 = 0%) (Figure 40).

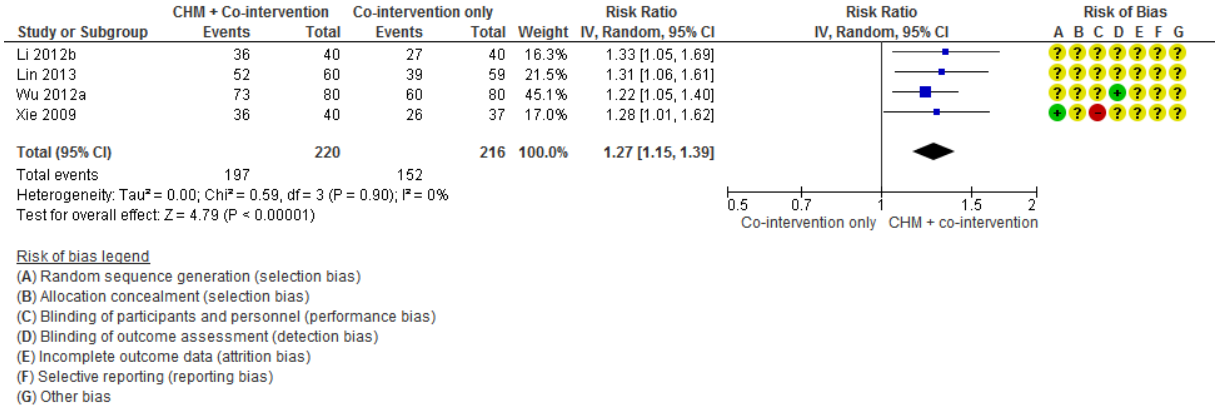


Figure 40. Global symptom improvement (short-term follow-up) for CHM plus co-intervention versus same co-intervention only

A six-month follow-up period was undertaken to evaluate the effects in two clinical trials (Shi 2012; Xiao 2015). Xiao 2015 conducted a four-arm trial, of which two of the arms were applicable in two subgroups namely, CHM with WM oral and external versus same WM (oral and external only); CHM with acupuncture and WM oral versus same acupuncture and oral WM only. Both clinical trials demonstrated no significant difference over WM oral and combined acupuncture treatment as well as comparison with same WM oral and external at (RR 1.13; 95% CI 0.96 to 1.35) and (RR 1.08; 95% CI 0.97 to 1.22), respectively. Overall, meta-analysis demonstrated that CHM was superior when combined with WM for global symptom improvement in the intermediate period (RR 1.08; 95% CI 1.02 to 1.14). No heterogeneity for the pooled data was shown ($I^2 = 0\%$) (Figure 41).

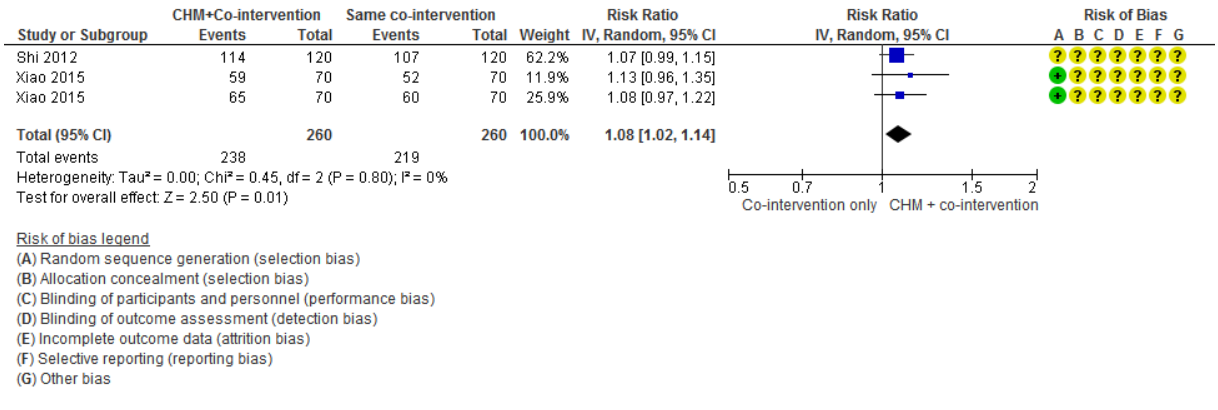


Figure 41. Global symptom improvement (intermediate follow-up) for CHM plus co-intervention versus same co-intervention only

Four studies assessed their patients for long-term follow-up of one year (Chen 2004; Lu 2003; Zhang 1996; Zhou 2005). Overall data showed CHM exerted significant difference over WM in the long-term period following treatment (RR 1.30; 95% CI 1.19 to 1.42) with heterogeneity at 0% (Figure 42).

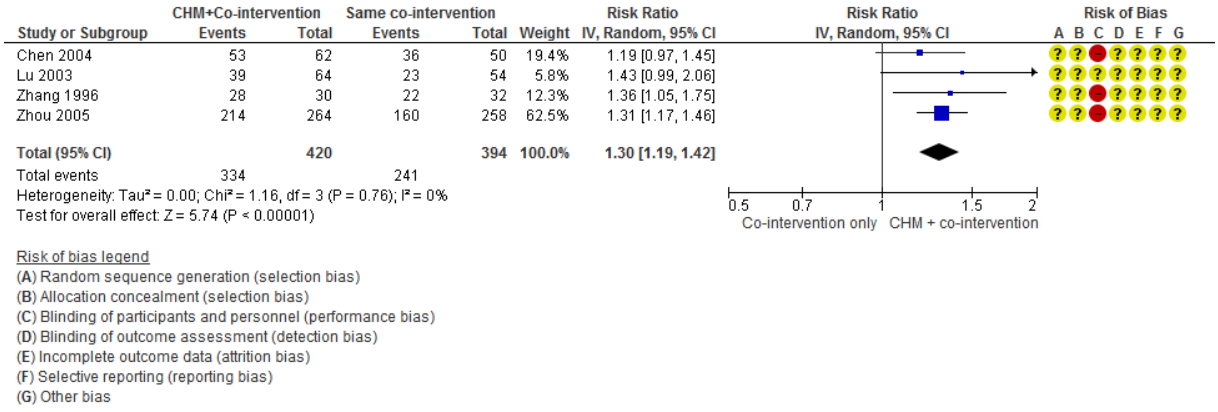


Figure 42. Global symptom improvement (long-term follow-up) for CHM plus co-intervention versus same co-intervention only

Owing to the differences in the co-interventions used in the 17 trials plus three comparisons from multi-arm trials, *post hoc* subgroup analyses were carried out. Seven subgroups were used to differentiate the use of different co-interventions combined with CHM, including Subgroup 1: CHM oral with WM oral versus same WM oral only (Cao 2014b; Chen 2011; Shi 2014; Tang 2008; Xiao 2015; Wu 2012a; Zhao 2012; Zhou 2005); Subgroup 2: CHM oral with WM (oral and external) versus same WM (Li 2008; Li 2012b; Li 2012c; Lu 1998; Shi 2012); Subgroup 3: CHM external plus surgery versus same surgery only (Liu 2004b); Subgroup 4: CHM oral with WM external versus WM oral and WM external only (Lu 2003); Subgroup 5: CHM oral combined radiofrequency versus same radiofrequency only (Chen 2004; Xie 2009); Subgroup 6: CHM combined with acupuncture and WM oral vs same acupuncture and WM oral (Xiao 2015); and Subgroup 7: CHM external with immunotherapy versus same immunotherapy only

(Zhang 1996). Among them, Xiao 2015 was assigned in subgroup 1 and 6 as it was a four-arm trial involving two relevant comparisons.

Among the different subgroups for immediate review after treatment, subgroup 2 (RR 1.22; 95% CI 1.06 to 1.40) (Figure 43, 4.5.2) and subgroup 3 (RR 1.42; 95% CI 1.06 to 1.91) (Figure 43, 4.5.3) featured CHM with WM co-intervention were more effective in improving global symptom right after AR treatment. Pooled data of the different subgroups demonstrated CHM with combined other therapies were superior to same therapies when used on its own (RR 1.32; 95% CI 1.06 to 1.64). However, substantial heterogeneity is embedded in the trials (I^2 = 84%) (Figure 43).

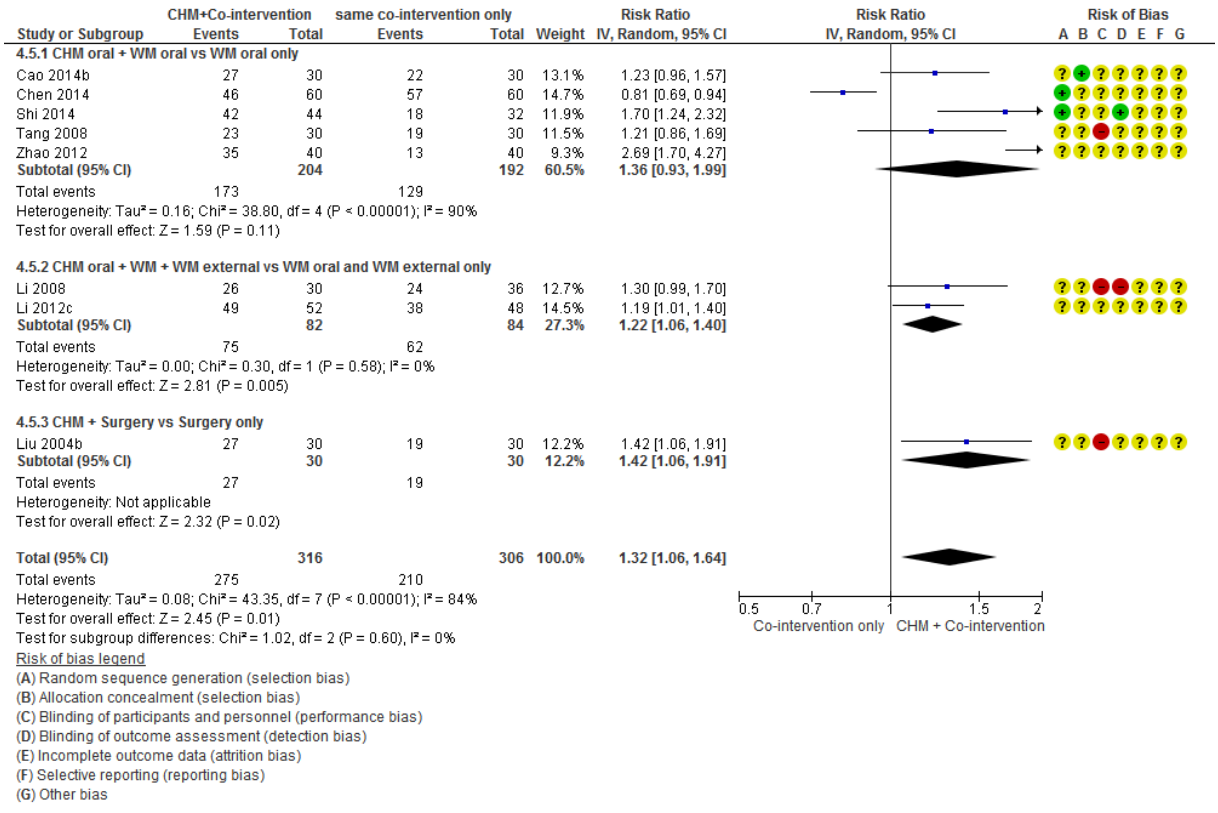


Figure 43. Global symptom improvement (immediate follow-up) *post hoc* subgroup analysis for CHM plus co-intervention versus same co-intervention only

Positive results are depicted for short-term outcome in global symptom improvement for CHM. Subgroups 1, 2 and 5 indicated CHM combined with WM were more effective in improving

overall symptoms than WM in this segment of *post hoc* analysis (RR 1.27; 95% CI 1.16 to 1.40) (Figure 44, 4.6.1 to 4.6.3). No heterogeneity was detected (I^2 = 0%) (Figure 44).

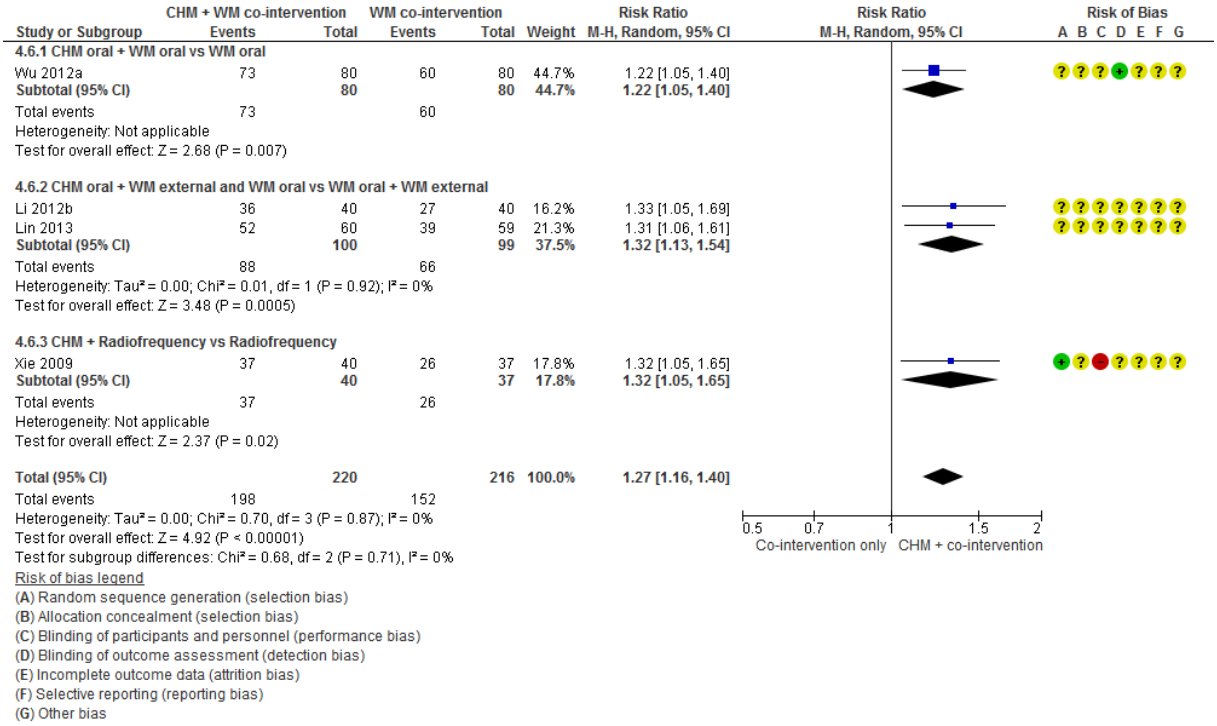


Figure 44. Global symptom improvement (short-term follow-up) *post hoc* subgroup analysis for CHM plus co-intervention versus same co-intervention only

When assessed over intermediate period up to six months; CHM coupled with WM also exerted significant effects when compared to WM only. Meta-analysis of these subgroups showed CHM combined group was more effective in global symptom scores at the end of the intermediate period (RR 1.08; 95% CI 1.02 to 1.14) with a low heterogeneity (I^2 = 0%). (Figure 45).

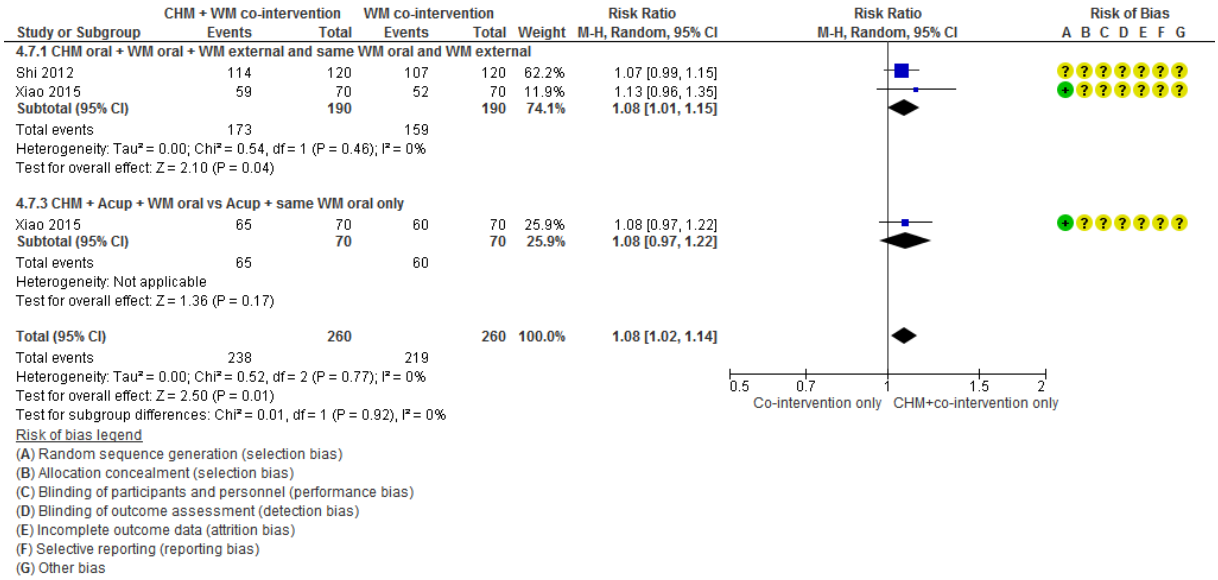


Figure 45. Global symptom improvement (intermediate follow-up) *post hoc* subgroup analysis for CHM plus co-intervention versus same co-intervention only

When assessed over long-term, global symptom improvement was highly positive with CHM combined group over different Western medicine co-interventions used alone (RR 1.23; 95% CI 1.15 to 1.32) (I^2 = 0%). No significant difference was detected for either CHM plus WM oral and external) versus same WM alone (RR 1.43; 95% CI 0.99 to 2.06) or CHM combined with radiofrequency versus radiofrequency only (RR 1.19; 95% CI 0.97 to 1.45) (Figure 46).

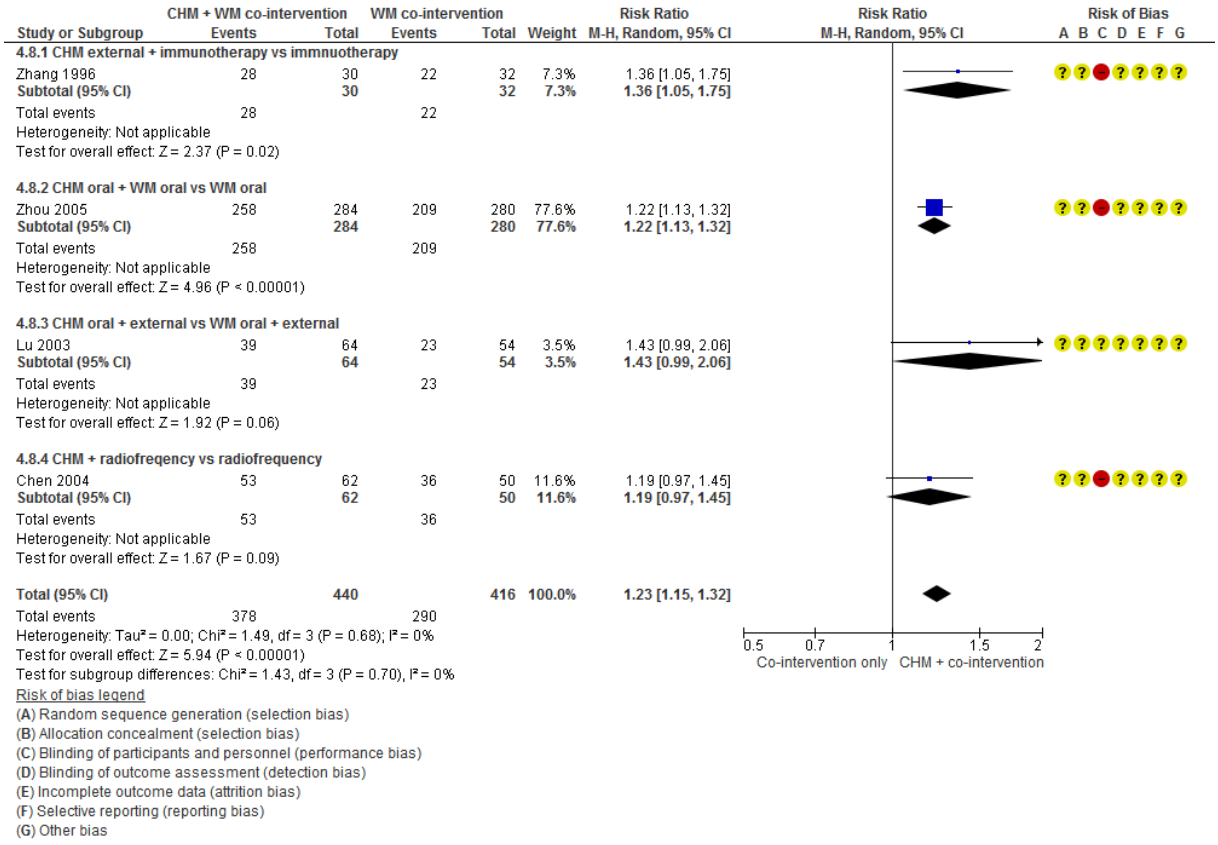


Figure 46. Global symptom improvement (long-term follow-up) *post hoc* subgroup analysis for CHM plus co-intervention versus same co-intervention only

Subgroup analysis was conducted for non-classified AR and PAR trials with and without syndrome differentiation. Two non-classified AR studies (Li 2012c; Zhou 2005) involving syndrome differentiation demonstrated significant difference existed when CHM plus co-intervention was compared to same co-intervention only (RR 1.21; 95% CI 1.13 to 1.30). Similarly, combined therapy in the trials without syndrome differentiation provided benefits to AR sufferers than same other therapy alone (RR 1.27; 95% CI 1.13 to 1.43). The heterogeneity for with and without syndrome differentiation AR subgroups was I^2 = 0% and I^2 = 63%, respectively (Figure 47).

Out of 17 studies, eight were involved in PAR clinical trials. Among the eight trials, only two trials employed the use of syndrome differentiation in CM to treat the patient in the trials (Li 2008; Tang 2008) while six PAR studies did not employ the use of syndrome differentiation

(Chen 2004; Lin 2013; Shi 2012; Shi 2014; Xie 2009; Zhang 1996). Both PAR trials with and without syndrome differentiation demonstrated positive outcomes in CHM combined group for improving global symptom, (RR 1.26; 95% CI 1.02 to 1.56) and (RR 1.27; 95% CI 1.09 to 1.49); respectively. Meta-analysis of the studies in the PAR and AR subgroup showed CHM were highly effective in improving AR global symptom as an adjunct therapy (RR 1.24; 95% CI 1.09 to 1.49). However, substantial heterogeneity is reflected in the pooled data (I^2 = 56%) (Figure 47).

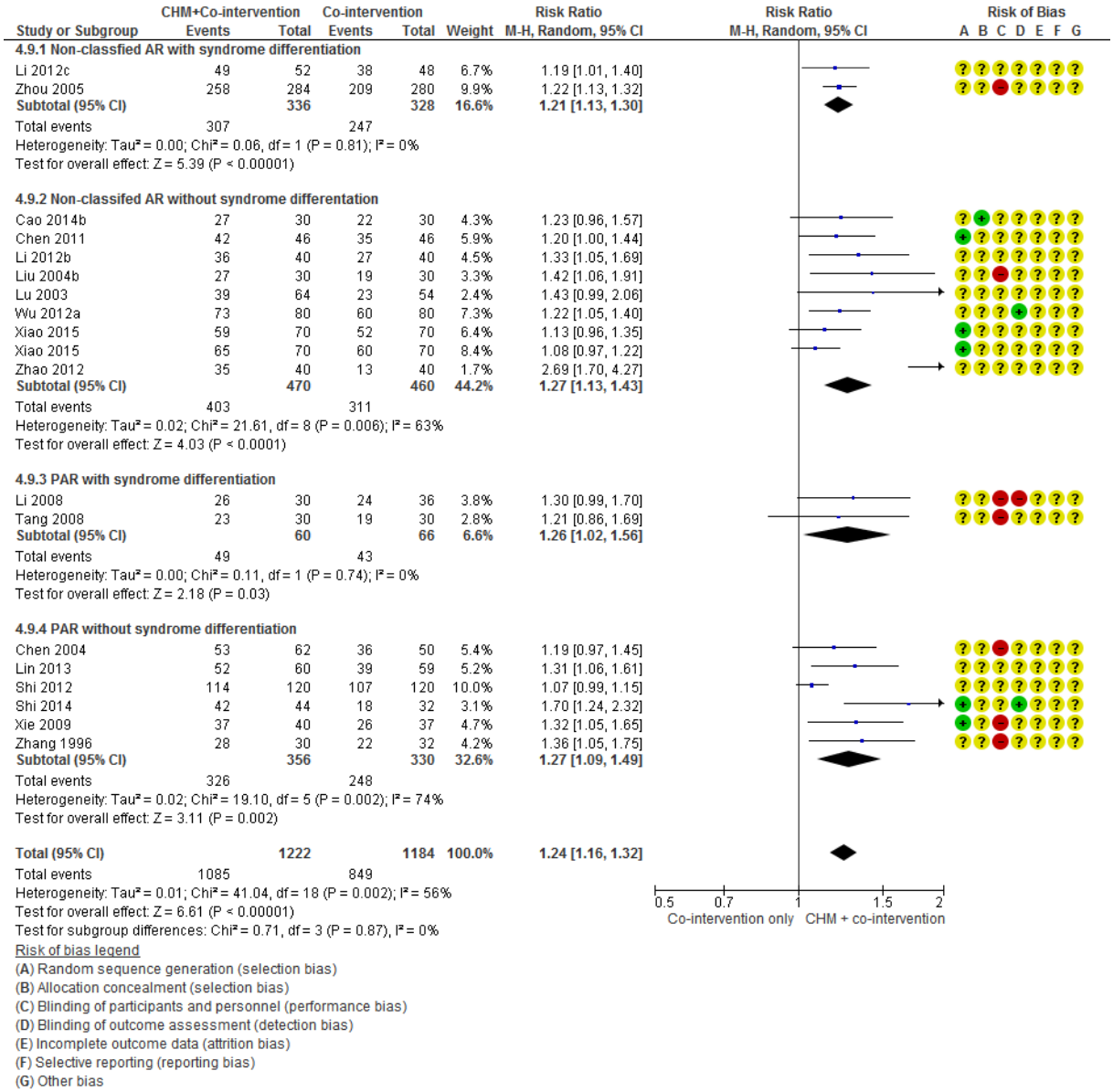


Figure 47. Global symptom improvement for PAR and non-classified AR subgroup analysis for CHM plus co-intervention versus same co-intervention only

Only one study Chen 2014 evaluated the changes of symptom score in immediate follow-up in the AR associated four-symptom category. Pooled data of immediate follow-up treatment showed that Cetirizine alone could reduce more symptom scores compared to combined group: changes in nasal congestion (MD -2.10; 95% CI -2.55 to -1.65), sneeze (MD -2.80; 95% CI -3.31 to -2.29), itchy nose (MD -2.03; 95% CI -2.48 to -1.59) and runny nose score (MD -2.52; -3.01 to -2.04).

Two studies were evaluated global symptom score for immediate follow up after treatment (Chen 2014; Shi 2014). CHM with WM co-intervention exerted more effects than WM co-intervention (SMD -1.39; 95% CI -1.93 to -0.85). However, substantial heterogeneity was observed (I^2 = 64%) (Figure 48).

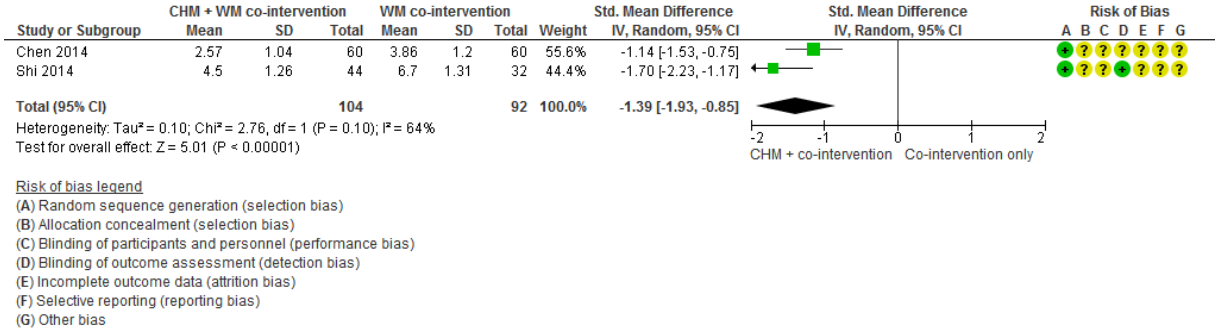


Figure 48. Global symptom score (immediate follow-up) for CHM plus co-intervention versus same co-intervention

The global symptom score over short-term follow-up for Lu 1998 demonstrated CHM combined group had significant difference over WM co-intervention alone (MD -8.50; 95% CI -9.72 to -7.27).

Another study (Lu 1998) also evaluated the outcome on the changes of scores but during short term follow-up. WM could reduce more scores for nasal congestion score (MD -4.36; 95% CI -5.07 to -3.65), sneeze (MD -8.01; 95% CI -9.17 to -6.84) and runny nose (MD -5.29; 95% CI

-6.11 to -4.46) than the CHM combined group. There was no significant difference for turbinate hypertrophy between the two groups (MD 0.00; 95% CI -0.38 to 0.38).

ii. Quality of Life

None of the included studies in this category assessed the quality of life after treatment.

iii. Medication consumption

No assessment was performed on the use of rescue medication in all 17 trials.

iv. Total serum IgE level

Only one study (Zhang 1996) compared CHM plus dust mite immunotherapy with same immunotherapy only and reported serum IgE level (Zhang 1996). Zhang 1996 tested the total serum IgE level for the CHM group right after two-month treatment but examined it for the control group at four months since the beginning of the immunotherapy. Thus, their results were not comparable.

v. Adverse events

Out of the 17 trials plus three comparisons from another three multi-arm trials, Lu 1998 reported four subjects suffered from stomach upset but did not mention whether they were in CHM combined with WM group or WM control group; one study (Shi 2014) reported no adverse effects were observed during the trials. The remaining 15 studies (Cao 2014b; Chen 2011; Li 2008; Li 2012b; Li2012c; Lin 2013; Liu 2004b; Lu 2003; Lu 2009; Shi 2012; Tang 2008; Wu 2012a; Xiao 2015; Zhao 2012; Zhou 2005) did not report any information related to adverse effects in their studies.

For those comparisons from the three multi-arm RCTs, the adverse events were not reported specifically for each arm. Therefore, the relevant information was reported under “v. Adverse events” of 5.4.2 CHM versus Western medicine.

5.5. Principal herbs used in RCTs

The total number of CHMs used in the RCTs treatment group was 552. All the trials used herbal formulations with the exception of three studies which employed the use of single herb to evaluate the effects on AR (Jung 2011; Matkovic 2010; Wu 2009). The rest of 59 included studies applied 59 different Chinese medicinal formulae. Six studies (Liang 2011b; Cao 2014b; Li 2012c; Li 2012b; Huang 2010; Ye 2015) used two formulae; while Lu 2009 employed three formulae for three different syndromes. Table 16 summarises the formulae names and the number of herbs in the 62 included studies.

Table 16. List of formulae and total number of herbs used in the included RCTS

No.	Study I.D.	Number of herbs	Formulae
1.	Baba 1995	8	Tsumura Sho-seiryu-to granule
2.	Bao 2013	8	Xiaoqinglong tang ampule
3.	Cao 2007	3	Cang'erzi granule
4.	Cao 2014b	8	Chuanxinlian tablets and Yupingfengsan granule
5.	Chen 2012	8	Xingbiwenningjiaoji
6.	Chen 2004	13	Yupingfeng decoction
7.	Chen 2014	3	Yupingfengsan granule
8.	Chen 2011	9	Yupingfengsan powder
9.	Gao 2009	3	Modified Lingguizhugan decoction
10.	Guo 2010	8	Qufengzhiyang liquid
11.	Han 2002	10	Bushenwenfei capsule
12	Hong 2005	9	Fufangbiyan decoction
13.	Hu 2002	11	Biminne capsule
14.	Huang 2008a	10	Bimin nasal drops
15.	Huang 2006b	7	Wenfeizhiliu pills
16.	Huang 2010	4	Jieminqufeng erhao granule/Jieminqufeng yihao granule
17.	Jiang 1997	8	Yufeng jianbi decoction
18.	Jin 2010	12	Kemin decoction
19.	Jung 2011	1	Fermented red ginseng capsule

No.	Study I.D.	Number of herbs	Formulae
20.	Lenon 2012	8	RCM-102
21.	Li 2012b	11	Cang'erzi san with Yupingfengsan
22.	Li 2012c	35	Qufengtongqiao Tang modified/ Bufeiqixuxing modified/Wenbupishen Huoxuetongqiao modified
23.	Li 2008	10	Xiaoqinglongtang & Yupingfengsan powder
24.	Liang 2011	14	Jiawei Buzhongyiqitang
25.	Lin 2013	7	Yupingfengsan extract
26.	Liu 2004b	8	CHM formula to nourish Yin & calm Liver
27.	Liu 2001	5	Dibiling nasal drops
28.	Lu 2011	8	CHM formula
29.	Lu 2003	10	Bimin formula
30.	Lu 2009	9	Modified Guizhi decoction
31.	Lu 1998	9	Modified Wenfeishiliu/Buzhongyiqi decoction/Jingui Shenqi decoction
32	Luo 2013	12	Qingretongqiao san
33.	Matkovic 2010	1	*Astragali* extract
34.	Peng 2001	12	Biminling decoction
35.	Peng 2004	7	Shetizhiqiu granule
36.	Qin 2006	13	Biyan granule
37.	Qiu 2012	12	Xiaoqinglongtang Jiawei
38.	Shen 2004	4	Yupingfengsan droppil
39.	Shi 2014	8	Xiangju capsule
40.	Shi 2012	5	Tongjiaobiyan Jiaonang
41.	Sun 2014a	9	Xiaofeng granule
42.	Tang 2008	6	Sijunzitang
43.	Wang 2000a	6	Tuimin nasal drops
44.	Wu 2012a	1	*Flos Magnoliae* volatile nano-liposome nasal drops
45.	Wu 2009	10	Xin Qin Keli
46.	Xiao 2015	11	Yupingfengsan decoction
47.	Xie 2009	5	Chinese herbal granule
48.	Xin 2005	14	Qi-boosting CHM
49.	Xue 2003a	18	CHM extract capsule

No.	Study I.D.	Number of herbs	Formulae
50.	Xue 2003b	18	CHM extract capsule
51.	Yan 2011	11	Modified Yupingfengsan
52.	Yang 2004	9	Xinqin capsule
53.	Ye 2015	13	Guizhitang Jia Huangmafuzixixin tang
54.	Zhang 1996	7	Tongqiaobiyan granule
55.	Zhang 2007b	6	Biyan granule
56.	Zhao 2012	6	Xingbiningjiaoji
57.	Zhao 2009	9	Jianbi mix
58.	Zheng 2007	6	Shi-Bi-Lin extract capsule
59.	Zhong 2013	9	Xinzhi nasal drops
60.	Zhou 2001b	16	CHM formula
61.	Zhou 2005	6	Tuomintongqiao capsule
62.	Zou 2012	5	Qufengtongqiaotang

The top ten most frequently used Chinese herbs in the RCTs were Huang Qi (*Astragali Radix*) (in 41 studies), Fang Feng (*Saposhnikoviae Radix*) (in 39 studies), Xin Yi (*Magnoliae Flos*) (in 31 studies), Bai Zhu (*Atractylodis Macrocephalae Rhizoma*) (in 31 studies), Cang Er Zi (*Xanthii Fructus*) (in 27 studies), Gan Cao (*Glycyrrhizae et Rhizoma*) (in 26 studies), Bai Zhi (*Angelicae Dahuricae Radix*) (in 26 studies), Xi Xin (*Asari Radix et Rhizoma*) (in 24 studies), Dang Shen (*Codonopsis Radix*) (in 17 studies), Wu Wei Zi (*Schisandrae Chinensis Fructus*) (in 13 studies) (Figure 49).

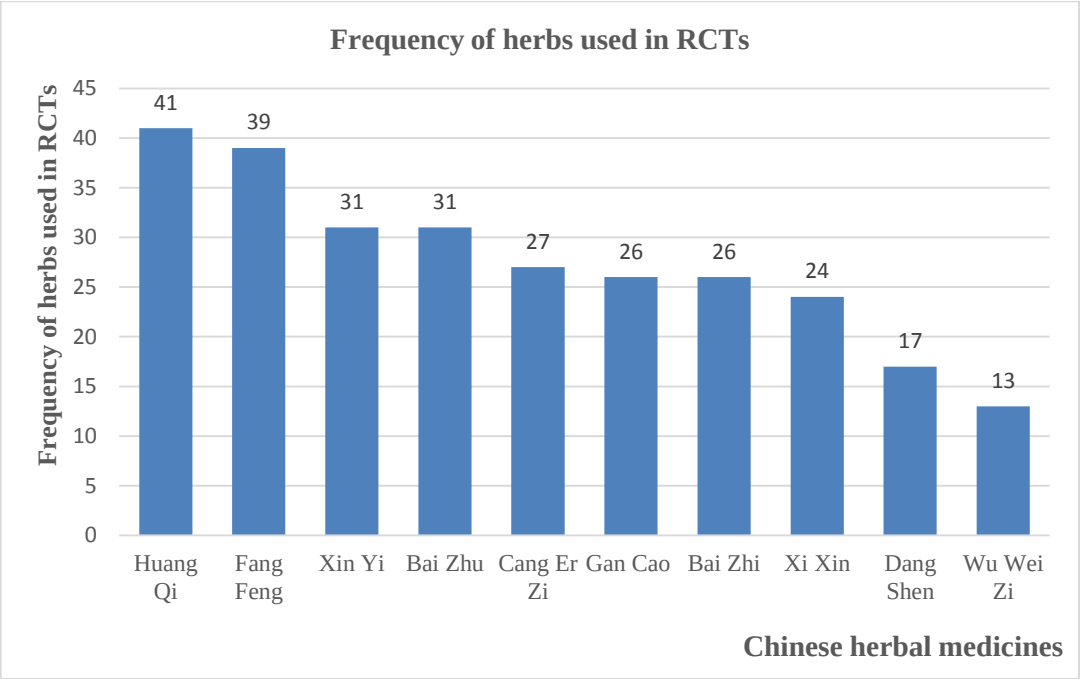


Figure 49. Top 10 herbs used in RCTs in the systematic review

5.6. Discussion

The current review identified 62 included studies for CHMs compared with placebo or Western medicine, with or without co-interventions. An overview of the clinical effects of CHM in the management of AR is outlined in Table 17.

Table 17. Summary of clinical effects of CHM in the management of AR

Comparisons	No. of RCTs	Global symptom improvement (No. of RCTs)	Quality of life	Rescue medication use	IgE	Adverse events
CHM vs Placebo	7	+ (n=1)	-	+ (n=4)	N/A	mild (n=7)
CHM vs Western medicine	37	+ immediate (n=15) short-term (n=14) intermediate (n=4)	N/A	N/A	-	mild (n=20)
CHM + co-intervention vs Placebo + co-intervention	1	N/A	-	N/A	N/A	mild (n=1)
CHM + co-intervention vs same co-intervention only	17 Plus one comparison of Chen 2004, Xie 2009, Zhang 1996 and Xiao 2015	+ immediate (n=9) short-term (n=4) intermediate (n=3) long-term (n=4)	N/A	N/A	-	mild (n=2)

Notes: N/A: data not available; - : no significant difference between two groups; +: favours CHM intervention.

CHM for the management of AR was evaluated on five domains in the SR. In the category of CHM vs placebo, only Baba 1995 evaluated global symptom improvement based on the changes in the severity nasal symptom, Sho-seiryu-to was found to have significant difference when compared to placebo. Positive global symptom improvement was demonstrated in studies conducted across the immediate (n=15), short-term (n=14) and intermediate (n=4) follow-ups. CHM used in these trials indicated strong clinical effects over Western medicine. Positive outcomes for CHM were also featured strongly over Western medicine. The use of CHM in oral or external exhibited its clinical effects over WM oral and/or external except for controls such as radiofrequency and immunotherapy. In the category of the CHM plus co-intervention versus same co-intervention only, unequivocal clinical effects were demonstrated across all periods evaluated. When employed with or without syndrome differentiation for both PAR and non-classified, there was a clear indication of favour towards CHM experimental group.

Limited number of studies in the subgroup for combined therapy of radiofrequency for Chen 2004 and subgroup CHM plus acupuncture and WM oral verus same acupuncture and WM oral rendered insiginificant outcomes. When CHM is combined with other therapies, CHM exerted strong and prolonged clinical effects over all durations for treatment as an adjunct therapy.

For quality of life assessment, only six studies (Hu 2002; Jung 2011; Lenon 2012; Matkovic 2010; Xue 2003a; Zhao 2009) in the category CHM versus placebo and one in CHM plus intervention versus placebo plus same co-intervention evaluated the participants after treatment. CHM was found to be comparable to placebo in Hu 2012, Jung 2011, Lenon 2012 and Matkovic 2010. It was also discovered that CHM exerted positive impact on SAR in managing the emotional aspects of SAR which Xue 2003a assessed in section two of RQLQ. Only the Zhao 2009 trial used SF-36 questionnaire

Only four studies in the CHM versus placebo category and one trial in CHM plus intervention versus placebo plus same co-intervention only category evaluated the consumption of rescue medication. The pooled data indicated that rescue medication usage were not significant when CHM was compared to placebo groups, with or without co-intervention. None of the rest of the trials utilised rescue medication in their assessment.

The assessment of the total IgE serum was conducted by five studies in CHM versus placebo category, four of the studies reported insignificant differences in the levels of IgE between the groups. Similarly, for CHM plus co-intervention versus same co-intervention category, data for control were not provided in Zhang 1996. Further meta-analysis could not be carried out owing to lack of information.

Nearly half of the RCTs reported on adverse events, with 30 out of 62 reported information on adverse events in either the control and/or treatment or in both groups. In the CHM versus

placebo category, trials reported adverse events; seven trials reported in the category of CHM versus placebo; 20 studies in CHM versus WM, one study in category of CHM versus co-intervention versus placebo plus same co-intervention and 2 studies in the category CHM plus co-intervention versus same co-intervention only. In terms of adverse symptoms experienced by the participants, minor adverse events were observed in the CHM group were headache, stomach upset and oedema in treatment groups. However, in regards to the control groups, the use of WM appeared to exert stronger adverse effects on general unwellness ranging from fatigue, somnolence, and dry mouth syndrome to epistaxis. Systemic effects were observed with patients experiencing elevated blood pressure and palpitations with WM. CHM seemed safer as reflected in the meta-analyses; however, the lack of data in at least 50% of the studies may render an inaccurate analysis. Caution is required in the interpretation in this aspect.

Chapter 6 Results II – Review of experimental studies

Based on the findings from SR, five herbs were selected from the top ten herbs most frequently used list from the investigation which include; Huang Qi (*Astragali Radix*), Fang Feng (*Saposhnikoviae Radix*), Xin Yi (*Magnoliae Flos*), Cang Er Zi (*Xanthii Fructus*), Xi Xin (*Asari Radix et Rhizoma*). The WHO has developed monographs of some selected medicinal plants; of which only two of the herbs Huang Qi and Xin Yi have been included in the WHO monographs. This chapter reports the review outcomes in the mechanisms of actions of herbs in recently published literature of experimental studies as well as WHO selected herbs. This chapter examines the immunopharmacological efficacies of five popular herbs used for treatment of AR in CM; exploring their phytochemical, pharmacological and pharmacokinetic effects and pathways that extend beyond nasal allergy. Toxicological evidence of herbs such as Cang Er Zi and Xi Xin is also reviewed.

6.1. Mechanisms of actions of WHO-endorsed herbs

The chemical compounds and the pharmacological actions of Huang Qi and Xin Yi provided in WHO monographs are summarised in the table below (Table 18).

Table 18. Mechanisms of actions of WHO selected herbs

Herbs	Chemical Compounds	Pharmacological actions	References
Huang Qi (*Astragali Radix*)	Triterpene saponins (Astragalosides I-X and isoastragalosides I-IV) Polysaccharides	• Immunopotentiating effects • Immunostimulant activities • Cardiovascular effects • Anti-viral effects	WHO (1999)
Xin Yi (*Magnoliae Flos*)	Magnolol Honokiol Isoquinoline Alkaloid Magnocrarine Cadinol 1,4-cineole p-cymene β-eudesmol Geraniol	• Anti-allergic effects • Anti-asthmatic effects • Anti-bacterial effects • Anti-gastric effects • Anti-inflammatory effects • Anti-vascular effects • Anti-oxidative effects • Anxiolytic effects • Cardiovascular effects • Muscle relaxant effects	(WHO, 2009)

The compound of Xin Yi, magnolol was discovered multiple effects: anti-vascular resistant, anti-asthmatic, anti-bacterial, anti-gastric, anti-inflammatory antioxidative, anxiolytic and a muscle relaxant (WHO, 2009). Huang Qi manifested cardiovascular effects, immunopotentiating, immunostimulatory and antiviral activities (WHO, 1999). In terms of cardiovascular protection, magnolol appears to have an impact on coronary circulation and vascular resistance. Although no change to the blood pressure and coronary flow velocity was detected, but decreased blood pressure vascular resistance was significant with 10^{-4} g/kg (WHO, 2009). Magnolol also could inhibit norepinephrine-induced phasic and tonic contractions in rat thoracic aorta *in vitro*. Huang Qi also exhibited cardiovascular activity. Enhanced contractility and contraction amplification of models' hearts were detected. Latent inverted and biphasic T waves and prolonged S-T intervals response after intraperitoneal injection of Huang Qi were observed three to four hours in dogs (WHO, 1999). Saponins in Huang Qi exerted inotropic effects on cultured murine myocardial cells, suggesting a modulation of sodium and potassium ATPase exchange uptake (WHO, 1999).

The combined compounds, honokiol and magnolol extracted from the bark of Xin Yi, both inhibited the growth of *Actinomyces visccosus* ATCC 19246, *Streptococcus mutans* Ingbritt and *Streptoccoccus sobrinus 6715* with a low dose of bacterium concentration. The extract of the bark Xin Yi and magnolol were also able to inhibit the growth of Helicobacter Pylori. Anti-microbial activities of both compounds have marked effects (MIC, 25.0 μg/ml) against *Actinobacillus, Actinomycetemcomitans, Porphyromonas gingivalis, Prevotella intermedia, Micrococcus luteus* and *Bacillius subtilis* but not against *Shigella flexineii, Staphylococcus epidermidis, Eneterobacter aerogenes, Proteus vulgaris, Escherichia coli* and *Pseudomonas aeruginosa* (WHO, 2009).

Anxiolytic activity and muscle relaxant were also produced with honokiol and magnolol. Honokiol was discovered to possess 2.5 to 5.2 times more potency in anxiolytic effects than magnolol although both compounds could enhance the potentiating effect of γ-aminobutyric acid on [3H]flunitrazepam binding with EC_{50} value of 0.61 μM and 1.6 μM (WHO, 2009). Honokiol was the main chemical compound to contribute to the anxiolytic effect. Sedation, ataxia, muscle relaxation and a loss of righting reflex were also associated with magnolol *in vitro* with intraperitoneal administration (0.0-500 mg/k bw) (WHO, 2009). Other effects highlighted in the WHO monographs were discussed within the subpoints.

6.2. Anti-inflammatory and anti-allergic effects

Not all the herbs were screened for its chemical phenotypes on immunomodulatory effects. This was due to the limited studies that had undertaken analysis on the chemical structure of herbs. However, many studies have studied the chemical phenotypes and its contribution to the biological systems of diseases. Three herbs namely; Xi Xin, Xin Yi and Fang Feng were found to suppress cytokines-mediated inflammatory cascades. Inflammation is a common denominator in many chronic diseases and allergic diseases alike.

Fang Feng contains naturally-occurring chromones namely; prim-*O*-glucosylcimifugin (GC), 4′-*O*-β-D-glucosyl-5-*O*-methylvisamminol (GV), cimifugin (C), sec-*O*-glucosylhamaudol (GH), and 5-*O*-methylvisamminol (MV) (Chin, Jung, Chae, Yoon, & Kim, 2011; Dai et al., 2008; Okuyama et al., 2001). Coumarins, especially both furanocoumarins and pyranocoumarins were also available in the roots of this plant. GC, C, MV and coumarin anomalin, appeared to exert considerable inhibition in major inflammatory pathways such as NF-κB, mitogen activated protein kinases (MAPKs), CREB and NO production. Anti-inflammatory effects of Fang Feng in arthritic rats revealed significant decline in the arthritis score for pain and swelling with a reduction of the inflammatory cytokines levels, although

suppression of the TNF-α and IL-1β was only observable on rats with a higher dose of Fang Feng (Kong et al., 2013). PGE_2, a by-product of the cyclooxygenase (COX) pathway, was also decreased in both sera and joints. Evidence suggested Fang Feng deactivated NF-κB binding, facilitated by the suppressions of signal-transduction inflammation and induced by TNFα-mediated phosphorylation of ERK, JNK and p38 which were amplified (3.2, 2.8 and 2.6 fold, respectively) in both collagen-induced arthritic rats and human fibroblast-like synoviocytes (Kong et al., 2013). The inhibition of phosphorylated MAPKs phosphorylation-extracellular signal-regulated kinases (- ERKs), c-Jun NH (2) terminal kinase (JNK), and p38 was due to the action of GC. Among all the MAPK subtypes, p-JNK, was discovered most effectively suppressed.

Interestingly, although the chromone GC in Fang Feng was an effective inhibitor of NO and iNOS production, however when compared to C and MV, both the former and latter were by far stronger than GC in exerting anti-inflammatory effects (B. Zhao, Yang, Yang, & Liu, 2012). Fang Feng chromones and anomalin (a pyranocoumarin), were highly effective against acute and chronic inflammation. GC, in particular, counteracted the lipopolysaccharides (LPS)-induced inflammation in severe pulmonary inflammatory disorder manifested in acute respiratory distress syndrome (N. Chen, 2013). *In vivo* and *in vitro* results demonstrated GC attenuated LPS-induced cytokine levels; TNF-α, IL1β and IL6 were far lower in the GC group as compared to the control group (B. Zhao et al., 2012). Aside from Fang Feng anomalin-mediated inhibitions on inducible nitric oxide synthase (iNOS), COX-2, TNF-α and IL6, anomalin was also responsible for the deactivation of the transcriptional onset of NF-κB 9 in LPS-induced RAW 265.7 cells (S. Khan et al., 2011). Cytoplasmic expressions of IκBα were drastically reduced, along with subunits of NF-κB, p50, p65 and c-rel being translocated, indicative of anomalin obliterating NF-κB-DNA binding activities. Although anomalin was able to interrupt protein synthesis of IκBα phosphorylation, there was no inhibitory effect on

the protein-initiating factor, eIG2α phosphorylation. Notably, anomalin was also effective against acute and chronic inflammation associated with hyperalgesia and allodynia. It is common in allodynia, elevated expressions of MARK-ERK and p38 signalling and nuclei translocation correspond to activation of the CREB pathway (Crown et al., 2006). The release of these pro-inflammatories cytokines and pro-nociceptive mediators induced prolong pain in chronic inflammation. Anomalin interference in the cell-signal transduction particularly NF-κβ, MARK-ERK and p-38 expressions was exponentially reduced, in effect abolishing the CREB-DNA phosphorylation activity (S. Khan, Shehzad, Chun, & Kim, 2013).

Similarly, GV, GC, C and GH also exhibited evidence of being matrix metalloproteases (MMP) inhibitors (L. Li et al., 2015). Both matrixins such as MMP-2 and MMP-9 are responsible for clearing collagens fragments generated by collagenases in tissues repair and remodelling. Enhancement of both MMP-2 and MMP-9 activities induced by the IL8 secretion were inherent biomarkers of cancers (Riveiro et al., 2010). GV, GC, C and GH indicated a clear dose dependent inhibition in *in vitro* MMP-assay, IC_{50} at 15.6, 108.87, 313.25 and 344.4 μM, respectively (L. Li et al., 2015). GV was the strongest inhibitor of MMP-2. Yet in another study reported amongst the 11 herbs tested, Fang Feng was obvious in suppressing MMP-9 (M. H. Lee et al., 2008).

Both Xi Xin and Xin Yi are famed for its effectiveness in treating nasal allergy in CM. Methyleugenol (MEG), a genotoxic and cytotoxic compound in Xi Xin, manifested early phase anti-allergic effects by targeting signalling domains in mast cell activation. MEG effectively suppressed IL4, a cytokine driver for Th2 differentiation, influencing its effect on mucus secretion, IgE production and curtailing TNF-α expression of endothelial molecules adhesion and granulocyte migration in late phase inflammation of AR (Tang et al., 2015). Traditional theory of IgE receptor signalling established that antigen binding of FcεRI β and γ chains at the

onset acute inflammation was initialised by a Scr tyrosine kinase Lyn phosphorylation at immune-receptor tyrosine-based activation motifs (ITAMs) and resulted in the recruitment of spleen tyrosine kinase (Syk), in effect, triggering the enzymatic phosphorylation of Scr kinases and transmembrane adaptor linker for activation of T cells via ERK complexes. Recently, other Src-family kinases, Hck and Fyn were discovered to be also involved in the signalling cascade other than Syk and Lyn (MacGlashan Jr, 2008). MEG inhibitory effect on Syk incapacitated the paired-phosphorylation of Lyn and Syk in the IgE downstream cascade, however Lyn was not inhibited (Tang et al., 2015). This correlates with findings that Lyn kinase which in fact, was not abundantly available to FcεRI and was considered a rate-limiting molecular species, whereas Syk was a highly expressed signalling element, varied with levels associated with IgE-mediated histamine release (MacGlashan Jr, 2008). Moreover, primary signalling domain for IgE receptor signalling rested in Syk, not Lyn, with the latter positive signalling via FcεRI ITAMs and Syk depended on much its availability to receptors, responsiveness to IL3 and Fyn catalytic activity (Bruhns, Frémont, & Daëron, 2005). In addition, MEG also diminished the rate limiting step of arachidonate cascade in leukotriene biosynthesis as well as supressing COX-2 expression and 5-lipoxygenase (LOX) phosphorylation, which in the process halted prostaglandin and leukotriene activities (Tang et al., 2015). This anti-allergic action of MEG imparted a vasodilator effect in AR and allergic asthma and could potentially block the anaphylactic effects of prolonged bronchoconstriction. In essence, MEG impeded Syk molecular signalling and disrupted the Lyn/Sky phosphorylation pathway, this molecular inhibitory mechanism on Syk could serve as a "switch" to turn off acute onset of AR and allergic diseases.

The volatile oils of Xin Yi in particular, VOMbp also possessed an immunological-regulatory effect on mast-cell histamine release (Kuan, 2011; T. Q. Xiong, Qin, & Shen, 2006). Oral administration of 0.01-1.0 g/kg body weight of aqueous extract of Xin Yi derived from both the

flowers and the bark significantly inhibited IgE-passive cutaneous anaphylactic reaction (WHO, 2009). Levels of plasma histamine *in vitro* inhibited the release from rat peritoneal mast cells and prevented systemic anaphylaxis in rats. Arthus reaction associated with types III hypersensitivity was also reversed due to the presence of magnolol in Xin Yi (WHO, 2009). This anti-inflammatory action could be used to treat depositions of antigen-antibody complexes.

The process of mast-cell histamine release, cytokines-mediated isotype class switching to IgE inducted by IL4 and IL13 and IL5-induced eosinophilic infiltration are all pathological processes of AR, asthma as well as in other allergic diseases. Although both IL4 and IL13 are implicated in IgE production, IL13 is not specifically involved in Th2 differentiation. IL13 essentially functions with IL4 to induce alternative macrophage activation, repair epithelial tissue, fibrosis and produce mucous production. In essence, IL4 acts as Th2 differentiation agent, whereas IL13 drives downstream effector responses (Kasaian *et al*., 2013). VOMbp apparently could induce inverse biomarkers IL4 in both early and late inflammatory phases. Early phase response to VOMbp upregulated IL4 with a reduction of IL13 in the peripheral blood, conversely, a reverse phenomenon was observed in the late phase reaction with decreased IL4 and elevated IL13, both attenuated IgE and impeded histamine release (Kuan, 2011). The anti-inflammatory effects of VOMbp seems to reinforce the biologic characteristics of IL4 and IL13 inhibiting the allergic cascade, although the VOMbp molecular kinetics is not understood in this aspect. In addition, oral administration of 0.01-1.0 g/kg body weight of aqueous extract of Xin Yi derived from both the flowers and the bark also significantly inhibited IgE-passive cutaneous anaphylactic reaction (WHO, 2009). The discovery of the inverse antagonist on IL13 and IL4 effect of VOMbp on mast cell-derived histamine levels in the peripheral blood, inhibition of anaphylaxis and the reversal of Arthus reaction could present a promising novel drug in inverse dual cytokine-antagonist in controlling IgE production and

anti-mast cell-histamine release in AR. The down-regulation of cytokine actions of Fang Feng, Xi Xin and Xin Yi could serve as a drug target intervention for acute and chronic inflammatories.

6.3. Analgesic and antinociceptive effects

The isolated structures of C, GH, GC and GV chromones of Fang Feng were responsible for the analgesic effects (Okuyama et al., 2001). Hamaudol with its algycone portion as well as ledebouriellol and divaricatol (both pyranochromones) also imparted an opioidergic effect by increasing pain threshold *in vivo* when administered with a high dose of GH (Chin et al., 2011). Evidence of prolonged pain threshold suggested the analgesic effects of Fang Feng corresponded to the anti-inflammatory effects. It was speculated that the opioidergic effect could be related to the mode of action on an opioid receptor in the central nervous system and its pathway, not on the peripheral nervous system pain-associated inflammation generally produced on the peripheral sensory nerve as naloxone counteraction of pain threshold in LPS-induced pyrexia *in vivo* (Okuyama et al., 2001). Fang Feng effectively deferred at a later time. The antinociceptive effects for acute model persisted for six hours after two hours of treatment while for the chronic models, the effects lasted for five days.

Pain signals stem primarily from voltage gated sodium (Na^+) channel. $Na_v1.8$ and $Na_v1.9$, are expressed selectively in damage sensing peripheral neurons (Wood, Boorman, Okuse, & Baker, 2004) while $Na_v1.7$ is expressed in the dorsal root ganglia and sympathetic neurons (Black, Frézel, Dib-Hajj, & Waxman, 2012). $Na_v1.7$, tetrodotoxin-sensitive (TTX-S), fast activating and fast-inactivating Na^+ channel, is closely related to congenital insensitivity to pain owing to loss-of-function mutations in SCN9A (a $Na_v1.7$ gene encoder) and is linked to pain in erythromelalgia as well as paroxysmal extreme pain disorder (Black et al., 2012). Pain is a comorbidity often associated with chronic inflammation. Analgesic evidence for Cang Er Zi

was notable in marked reduction of writhing and formalin-induced licking time in murine models at late phase response but not at the early phase. (Huang et al., 2011). The nociceptive effects could in part be due to decreased levels of iNOS and COX-2 expressions and the radical scavenging, reducing activity and liposome protection exerted by the phenolic compounds in Cang Er Zi, although the molecular mechanisms on pain channel are not understood. Similar analgesic effects were also present in Fang Feng, which was attributed to the chromones compounds in the roots of the herbs (Kreiner, Pang, Lenon, & Yang, 2016). In Xi Xin, MEG tonically inhibited $Na_v1.7$ with resting state at a holding potential of -120mV and inactivated state at a holding potential of -60mV, in a concentration and voltage dependent manner. Peripheral nerve Nav1.7 was inhibited with an IC_{50} of 295 μmol/L at a -100mV holding potential. In order to gain the therapeutic effect of RA-MEG in emitting an average tonic inhibitory outcome, the receptivity of the receptor interaction to the concentrations of MEG was 1:1. Higher concentration of MEG evoked greater potency of inhibition at higher stimulus frequencies. Interestingly, Xi Xin exhibited the same effect as anticonvulsive drugs at interacting with $Na_v1.7$ channel inactivation state in negative potentials and displayed double the depolarizations in concentration dependent manner and recovery from inactivation state in the $Na_v1.7$ channel was also slower with higher concentration. These results suggested Xi Xin might effectively inhibit the sustained or transient high frequency bursts in peripheral nerve commonly associated with neuropathic pain (Z. J. Wang, Tabakoff, Levinson, & Heinbockel, 2015).

No clinical studies have directly evaluated Xin Yi and Huang Qi for any therapeutic effects for analgesia and antinociceptive conditions.

6.4. Anti-oxidative and anti-proliferative effects

The modulatory effects of Astragaloside-IV (AS-IV) in Huang Qi, magnolol in Xin Yi and MEG in Xi Xin were able to confer both neuroprotective and anti-oxidative effect. Oxidative stress is a result of excessive production of ROS. ROS accumulation often causes oxygen and glucose deprivation in cortical neurons, hippocampus and/or cerebrum, triggering an inflammatory reaction commonly seen in cerebral ischemia, hypoxia and memory deficits associated with dementia (S. Y. Kim et al., 2015). The neuroprotective effects of AS-IV in Huang Qi improved spatial learning and memory deficits in rats with chronic cerebral hypoperfusion. 8-hydroxy-2'-deoxyguanosine expression, an oxidative DNA damage marker commonly associated with aging and dementia; astrocyte as well as activated microglia in hippocampus were reduced markedly in AS-IV treated rats (20 mg/kg dose) (S. Y. Kim et al., 2015). Further reduction of detectable loss of hippocampal neurons and the thickness of this region also offered a glimpse of the efficacy of AS-IV in diminished memory models. Notable levels of superoxide dismutase (SOD) indicated increased ROS activities and presence of elevated malondialdehyde (MDA) also presented lipid peroxidation, which could cause protein modification in the DNA strands. At a transcriptional level, AS-IV was able to regulate activity of nuclear factor erythroid 2 (Nrf2), a regulator of anti-oxidant genes which binds to anti-oxidant response element (ARE), a promoter region of cytoprotective genes (Gu et al., 2015). Nrf2 is a master regulator of the cytoprotective genes responsible for exerting a dual effect. Activation of Nrf2 is mediated by the epidermal growth factor receptor (EGFR) signalling pathway, responsible for proliferation, growth and survival of cells (Abbas et al., 2012). Subsequent ubiquitination of Nrf2 is triggered by a disassociation from cyctolic inhibitor of Nrf2, an adaptor protein, facilitated by Nrf2Ser-40 phosphorylation (Abbas et al., 2012). This mechanism activates ARE gene expression that essentially promoted cell apoptosis, decreased Nrf2 and cell survival. On the other side of the coin, unrestrained activation of Nrf2 as a result of accumulation of Nrf2 in nucleus could reverse the effect of cell apoptosis and increase cell

survival. AS-IV revealed strong effects in inducing Nrf2 Ser-40 phosphorylation and nuclear localization and promoted ARE dependent genes while inhibiting ROS accumulation in cortical neurons. It was suggested that the activation of Nrf2 was dependent on the "transactivation" of EGF-EGFR signalling network as evidenced by the increased heparin-binding-EGF growth in AS-IV treated neurons, thus inhibiting oxygen and glucose deprived or re-oxygenated models, promoting ROS scavenging ability and activating Nrf2 in the wake of promoting apoptosis (Gu et al., 2015).

Aberrant levels of the antioxidant defence system in SOD, glutathione, catalase and glutathione peroxidase are hints of imbalance between these anti-oxidants and ROS. This imbalance triggers mutagenic transcription, promotes atherogenicity, activates cytokines downstream inflammation and produces plague depositions (Pisoschi & Pop, 2015). Neuronal hypoxic and ischemic cells, when treated with MEG, experienced an increase of radical scavenging activity with IC_{50} 13.7 μM (Choi et al., 2010). In comparison to vitamin C at 3.6 μM, MEG by far exerted a stronger anti-oxidative effect. Anti-oxidant enzymes, SOD and catalase were upregulated *in vitro*, with abnormal levels of superoxide ions and ROS substantially suppressed, this facilitated a reduction of cerebral infarct volume. The anti-oxidative effect of MEG in Xi Xin could be the key to deterring further cerebral cellular damage in lipids peroxidation and protein degradation induced by accumulation of ROS in ischemia and post–ischemic reperfusion injuries.

Hypoxia-induced cell injury in cortical neurons-astrocyte generally exposed cells to lactose dehydrogenase A release, commonly associated with induced apoptosis, affected invasive and spheroid growth tumours, reduced expression of MMPs and cancer-stem like cells markers (Maftouh et al., 2014). Treatment with 10 and 100 μM significantly reduced potassium cyanide-induced lactose dehydrogenase release in *in vitro*. In addition, in septicaemia, *in vivo* models

administered with magnolol before and after induction of sepsis by cecal ligation and puncture, survival rates remarkably improved with the pretreatment models (WHO, 2009). Overall intensity of lipid peroxidation in plasma, liver and lungs of the models was reduced.

Magnolol in Xin Yi also appeared to exhibit antioxidative effect extending cardioprotective activities. Myocardial ischemia and reperfusion injury was discovered to have been substantially reduced when early administration (10 minutes) before the incidence of left coronary artery occlusion (45 minutes) (WHO, 2009). The duration and the severity of the occlusion reduced the mortality and the ventricular fibrillation. After one hour of perfusion, levels of SOD anion and myeloperoxidase production as well as both primary indexes for neutrophil infiltration in ischaemic myocardium, reduced the infarct size. In addition, effects of magnolol was able to counter a common side effect of balloon angioplasty known as restenosis (an intimal rethickening in the arterial wall) (WHO, 2009). *In vitro* results on cholesterol fed models with injection of 1 μg/kg body weight of magnolol over six weeks discovered inhibition of copper-induced low density lipoprotein oxidation in cholesterol fed models and reduced atheroma formation in the thoracic aortas. Intimal response was also reduced in high cholesterol models.

These potentiated active compounds of Huang Qi, Xi Xin and Xin Yi could provide a novel therapy for neurodegenerative, myocardial and ischemic diseases.

Cellular proliferation is synonymous in cancers and metastases. Naturally occurring compound (-)-xanthatin in Cang Er Zi, exhibited potent anti-proliferative effects in cancer cells. Cytogenic aberrations are results of amplification or deletion of topoisomerase (topo) IIα that cause chromosomal translocation or deregulation of gene expression (Jarvinen & Liu, 2003). It is an enzymatic biomarker for cellular proliferation in cancers, responsible for DNA cleavage during

genes transcription and the mitotic remodelling of chromatin in the cell cycle. Expression of topo IIα was influenced by p53 and retinoblastoma susceptibility gene product, pRB, with the latter exerting a bi-functional role in stimulating and deregulating topo IIα cleavage via stimuli-induced GADD45γ protein while the former exerted a deregulatory role on topo IIα in cell cycle at G1/S boundary (Kellner, Maxwell, Jensen, Gieseler, & Rudolph, 2002). Interestingly, (-)-xanthatin was discovered to catalytically inhibit topo Iiα and induce DNA damage *in vitro* in human breast cells and activating GADD45γ, of which was stabilised by generated ROS. DNA-SC conformation was relaxed and after 12-hour exposure to (-)-xanthatin, chromatin remodelling surfaced with the formation of γH2AX (a marker of DNA double strand break). It was posited that ROS generation was an important mediator factor for (-)-xanthatin's anti-proliferative activities via induction of GADD45γ (Takeda et al., 2013). In addition, (-)-xanthatin was also antagonistic against the effects of etoposide. Although the potential of Cang Er Zi compound (-)-xanthatin may be heralded as a new chemotherapeutic drug intervention for cancers, however its pharmakinetic and its toxicokinetic mechanisms have yet to be investigated further.

Natural occurring chemical compounds could provide a drug scaffold for existing cancer therapy. Panaxynol, an active component of Fang Feng root displayed traits of reinforcing conventional drug treatment for human mammary adenocarcinoma. The discovery of *in vitro* tests in combined therapy with chemotherapeutics; camptothecin (CAM), paclitaxel (PTX) and Fang Feng achieved a synergistic effect in the IC_{50} value. IC_{50} is a measure of the drug concentration causing a 50% inhibition of a desired activity in the cellular mechanism (Kuo, Lin, Huang, Shu, & Tsai, 2002). Synergistic effects with the combined treatment of chemotherapeutic agents, CAM or PTX on the four cancer cells demonstrated Fang Feng extracts effectively reduced the IC_{50} values of CAM and PTX in K562 and HL60, PTX in MCF7 and MDA-MB-468 cells as compared to chemotherapeutic agent(s) alone and increased the

percentage of proliferative activity (Tai & Cheung, 2007). Co-administration of Fang Feng with a lower dose of chemotherapeutic agents could effectively achieve the same anti-proliferative effect as compared to a high cytotoxic dose of CAM or PTX for treatment of cancer. Complete inhibitory effects were observed *in vitro* at 100 μM of panaxynol with evidence of cell cycle arrest from G0/G1 phases to S and G2/M phases was observed. Remarkably, the ratio of cyclin E mRNA was also significantly decreased *in vitro*. Co-administration with Fang Feng extracts and chemotherapeutics exhibited no cytotoxicity or side effects in *in vitro*. However, this antagonistic effect on cell proliferation is highly dependent on the dosages of Fang Feng extracts and the chemotherapeutic agents.

6.5. Immunoregulatory effects

The immunoregulatory effect of Fang Feng polysaccharides on the spleen proliferation index and spleen index as well as on the macrophage and its phagocytic rate showed marked difference in spleen proliferation index marker (H. Liu et al., 2008). No significant difference was observed in the spleen index even though spleen proliferation index were higher than the control. An obvious increase of the phagocytic rate and macrophage index in mice coincided with the increased doses, 250, 500 and 1000 mg/kg of Fang Feng polysaccharides administered. Lymphocytes subsets ratio for CD3+CD4 increased from 27.28 ± 2.30% (250 mg/kg dose) to 45.82 ± 1.54% (1000 mg/kg), while CD3+CD8+ was significantly as high as 17.44 ± 1.78% (250 mg/kg dose) but decreased by 13.22 ± 1.34% (1000 mg/kg dose). Significant differences were detected in subsets CD4+CD8+ ratio from 1.58 ± 0.18% (250 mg/kg dose) to 3.49 ± 0.29% (1000 mg/kg dose), as well as CD19+ from 10.42 ± 2.40% (250 mg/kg dose) to 15.15 ± 2.32% (1000 mg/kg dose) (H. Liu et al., 2008).

The polysaccharides of Huang Qi confirmed in *in vitro* and *in vivo*, at concentrations of 10 mg/ml increased T-cell function of mononuclear cells derived from cancer patients (WHO,

1999). The immunopotentiating effect in T-cell deficient cancer patients was fully corrected *in vitro*. Huang Qi polysaccharides were found to be able to reverse cyclophosphamide-induced immunosuppressant effect in rats. Enhanced IL2 activity generated lymphokine-activated killer cell activities *in vitro* (WHO, 1999). Further phagocytic activities also induced the antibody to a T-dependent antigen and polysaccharides are responsible for Th cells activities in both normal and immunosuppressed models. When countering cobra venom on immune function of treated mice and guinea pigs, treatment with Huang Qi polysaccharides increased levels of complement and neutrophil phagocytic activities as well as levels of neutrophils granular substances (WHO, 1999). Aside from immunopotentiating effects, the immunostimulatory effects were observable when human adults were treated with 15.6 g of oral dose of *Astragali* root for 20 days (WHO, 1999). Increased IgM, IgE, cAMP concentrations were detected. Huang Qi was also highly effective against coxsackievirus B myocarditis with enhanced natural killer cells response. The overall effects also stimulate interferons which are associated antiviral activities.

No clinical studies evaluated immunoregulatory effects on Cang Er Zi, Xin Yi and Xi Xin.

6.6. Anti-asthmatic effects

A shift of Th1 predominance to Th2 is a typical characteristic of airway hypersensitivity, inflammation, hyperresponsiveness and airway remodelling observed in exacerbation of AR with comorbidity of asthma. Influx of proinflammatory Th2 cytokines LI4, IL5 and IL13 initiate eosinophilic responses to proliferate mast cells and secrete chemoattractants, promoting the induction of B-cells towards IgE production. Prolonged amplification of these self-antigenic response triggered Treg cells. The phenotypic characteristics of Treg cells lie in CD4+CD25+Foxp3 whose key role is to suppress the activation and the effector functions of other, self-reactive and potentially pathogenic lymphocytes (Abbas et al., 2012). The reductive effect of Huang Qi on airway hyperresponsiveness was marked with the suppression of IL4,

IL5 and IL13 and increased Th1 cytokine INF-γ, elevated leukocytes, eosinophils, lymphocytes, macrophages and neutrophils levels as well as CD4+CD25+Foxp3+Tregs in bronchoalveolar lavage fluid. Reduction of collagen deposits, peribronchial fibrosis and mucous secretion in active murine models. Treg cells were increased by 17.9% at an oral dose of 10 mg/kg (Jin et al., 2013). It was posited that the bidirectional regulatory effects on cytokines could be due to the complex constituents of the *Astragali* polysaccharides in Huang Qi, thereby resulting in modulation of the hypersensitive airway structure.

As yet, the strongest anti-asthmatic effect was exerted by AS-IV, a major active constituent of Huang Qi, at mRNA level with expressions of Foxp3 (transcription factor) and peroxisome proliferation-activated receptor-γ (PPAR-γ). PPAR-γ is a nuclear receptor subtype responsible for regulating inflammatory cytokines cascade, with a secondary regulatory role in IgE and IgG production and GATA-3 and T-bet (both transcription factors) expressions in cell differentiation (Abbas et al., 2012). The latter transcription factors are master regulators of Th1 and Th2 cell differentiation. Increased expressions of PPAR-γ in bronchial submucosa, airway epithelium, and smooth muscles are commonly associated with asthma (Woerly et al., 2003). AS-IV decreased GATA-3 and increased the activity of PPAR-γ in asthmatic simulated models. The increase of activity of PPAR-γ implied a possible reversal of Th2 to Th1 to downregulate the effector cells and cytokines infiltration in airway allergy through inhibition of Th2 cytokines (S. M. Chen, 2014). The efficacy of Huang Qi was equivalent to rosiglitazone, a PPAR-γ agonist, *in vitro* (S. M. Chen, 2014).

Remodelling of the bronchial muscle in asthma is a typical response of the cytokines and chemokines as a result of mast cells activation and degranulation causing increased of deposits of extracellular matrix proteins (Bara, Ozier, Tunon de Lara, Marthan, & Berger, 2010). Calcium activities in tracheal smooth muscle were affected with decreased potassium outward

currents. Magnolol, a compound in Xin Yi, was discovered to reversibly increase the amplitude of the potassium outward flow and effectively increase the conductance of calcium activated potassium channels with effective concentration value of 1.5 μM of magnolol (WHO, 2009).

Xi Xin has longed been used for its anti-asthmatic effects in CM. There have been no studies that evaluated the anti-asthmatic effects of Xi Xin. Studies on anti-asthmatic effects of Xi Xin are always coupled with other herbs in formulae to determine its efficacy. In addition, no clinical studies have been conducted on Cang Er Zi and Fang Feng for anti-asthmatic effects.

6.7. Toxicological evidence

Of the five herbs, only two of the herbs, Cang Er Zi and Xi Xin, were found to possess toxic compounds. Dose-related toxicities and side effects of Cang Er Zi have arisen in recent literature (L. L. Chen, 2013; Yao, 2006; Yu et al., 2013). Diterpenoids glycosides, atractyloside (ATR) and carboxytractyloside (CATR) are the main toxic constituents. ATR and CATR toxicities often result in high dose-related incidences causing kidney damage which manifests haematuria, albuminuria, abnormal renal function and acute renal failure. Yu et al. (2013) demonstrated no acute toxicity was manifested at low dosages, however at higher dosages, acute toxicity was obvious for both raw and stirred-fried Cang Er Zi (Jiao Ban Chao Cang Er Zi, 搅拌炒苍耳子). Chronic toxicity was indicated in the fluctuating changes of blood nitrogen urea, serum creatinine with pathological changes in congestion and focal necrosis in the liver, renal tubules, lungs and heart after prolonged administration in both medium and high dosage mice groups. Obvious side effects of thrombocytopenia also emerged. The investigators (Yu et al., 2013) concluded that a single of administration of even 10 times the permitted highest daily dosage of Cang Er Zi (3 g to 10 g) as legislated by Chinese Pharmacopeia 2015 (Chinese Pharmacopoeia Commission, 2015) is safe. This experiment elucidated an observation that the lack of dose-dependent toxicity response relationship might have precluded the exposure time

and the possible toxicological pathways of both ATR and CATR of Cang Er Zi were not clarified. Despite its cytotoxic nature, Cang Er Zi still offers much potentiated use in the treatment of cancers and tumours.

Xi Xin is currently still used in the clinical practice of CM in China, Japan, Singapore, South Korea and Taiwan, although it is scheduled in Australia and parts of Europe such as Holland and England (Z. Z. Zhao et al., 2008). Xi Xin is indicated in the classical text Shennong's Classics of Materia Medica (Shen Nong Ben Cao Jing, 神农本草经) to release the exterior pathogen, dispel wind cold, clear nasal cavities warm the Lung and expectorate the lavages in the bronchial system (R. Hu, 2015). These connotative descriptions parallel respiratory conditions such as respiratory and comorbid conditions such cold, chronic sinusitis, cough, dyspnoea in chronic obstructive pulmonary disease, lavage congestion in lungs, and AR comorbid headache. Although Xi Xin genus belongs to the *Aristolochia* family, chromatographic fingerprint of this herb did not detect aristolochic acid I (AA-I) (Wagner, Bauer, Melchart, Xiao, & Staudinger, 2011). AA-I is a toxic component primarily responsible for drug-induced nephropathy, also known as Chinese herbal nephropathy (Rietjens, Martena, Boersma, Spiegelenberg, & Alink, 2005). However, recent literature study discovered that there are trace AA-I ranging from 3.1 mg to 26.6 mg in chromatography screening (Y. Liu, Gao, Wang, & Zhang, 2010), its amount is in fact negligible. It is confounding that both studies Y. Liu et al. (2010) and Wagner et al. (2011) revealed conflicting results on the toxicity of Xi Xin. Z. Z. Zhao et al. (2008) conducted a thorough study on the levels of AA-I in the different portions of Xi Xin in liquid chromatography–mass spectrometry and the comparisons of the potency of AA-I in different extracts. The aerial parts of Xi Xin was found to contain higher levels of AA-I than the roots and methanol extracts contained more AA-I than water extracts (Z. Z. Zhao et al., 2008).

The chemical constituents present in Xi Xin are estragole, MEG, elmicin, safrole, asaricine, croweacin and kakuol (Drew et al., 2002). The implicating toxic agents in Xi Xin are mainly due to safrole and MEG (C. Chen et al., 2009; Chiang et al., 2011). Both constituents are commonly found in foods; safrole derived from essential oils of sassafras, nutmeg, sweet basil, garden basil, tarragon, cinnamon, nutmeg, star anise, black pepper and methyleugenol from pimento, nutmeg, lemongrass, tarragon, basil, star anise and fennel (Rietjens et al., 2005).

Both safrole and MEG constituents share derivatives of alkenylbenzene and are both nephrotic and hepatic carcinogenic agents. MEG dose of 100 mg/kg and safrole 0.5% dose (in a dose dependent manner) were discovered to be carcinogenic when the glutamate pyruvate transaminase delta manifested marked increase in glutamate pyruvate transaminase mutations and Spi^- mutant frequency as well as positive proliferating cell nuclear antigen, a monoclonal antibody marker for preneoplastic lesions in the liver cells. A GC→CG transversion mutation in the treated male rats and an AT→TA transversion mutation in the female rats were observed, although incidence rates were not statistically significant compared to control (Jin et al., 2013). Safrole-glutamate pyruvate transaminase-mutant spectra also detected mutant changes with the predominant type of AT:GC transition being significantly present in the genome (Jin et al., 2011). Both these toxic agents could induce cytotoxicity and genotoxicity causing renal and hepatic failures.

Acute toxicity signs and symptoms manifested were convulsions, torpor, breathlessness and lack of appetite. Although water extraction was administered in high dosage, no obvious intraocular toxic reaction was detected with acute poisoning. The long-term toxicity of Xi Xin on hepatotoxicity and nephrotoxicity was also further evaluated *in vivo*, which demonstrated the degree of renal damage was relative to the dosage administered in two Chinese studies (W. X. Chen, 2009; J. J. Li, 2007). Severe hyperplasia, fibrosis, renal congestion and large amount

of inflammatory cell infiltration with marked renal tubular necrosis. Severe weight loss and reduction of appetite were associated with Xi Xin toxic signs and symptoms. Blood urea nitrogen (BUN) and creatinine (Cr) are primary markers for nephrotoxicity. BUN tests the clearance rate of the kidney by determining nitrogenous element in the bloodstream, Cr refers to the metabolic by-product of muscle metabolism excreted by urea. The category of the light-dosage rat models' biomarkers of BUN and Cr were similar to the control group. This indicated that light doses of Xi Xin extracts might take longer time for nephrotoxicity to take effect. Nephrotoxicity induced by Xi Xin was reversible in both medium and high dosage *in vivo* models. Morphological samples revealed only inflammatory cell infiltration with no delayed toxic reactions. Xi Xin-induced hepatotoxicity also corresponds to the relative dosage as investigated in another study (J. J. Li, 2007). Long-term administration with high dosage in rat models manifested an increase of the total bilirubin levels with little effect on the synthetic liver function. Severe pathological changes in high dosage group manifested large inflammatory cell infiltration and necrosis tissue in the liver, reversibility of hepatic injury was achieved once the administration of Xi Xin stopped. Long-term effects Xi Xin-induced renal and hepatic toxic injury were reversible within two weeks of cessation, regardless of the dosage (W. X. Chen, 2009; J. J. Li, 2007).

The instructive dosage of Xi Xin was noted in the Shennong's Classics of Materia Medica -(Xi Xin Bu Guo Qian, 细辛不过钱), which highlighted that dosage used in formulation should not exceed 3 g (R. Hu, 2015). Current Pharmacopoeia of China 2015 editon stipulated Xi Xin dosage should be administered within 1 to 3 g (Chinese Pharmacopoeia Commission, 2015). The toxic mechanism in relation to the dosages could essentially be compounded the types of extractions in the preparation of this herb. Three types of extractions were tested on the mice: supercritical extract, volatile oil extract and water extract, measuring the median lethal dose (LD_{50}). Dose-response experimental results demonstrated LD_{50} and CI limit of volatile oil and

supercritical fluid extraction were 86.9 g $kg^{-1} \cdot d^{-1}$ (62.2~120.8 g $kg^{-1} \cdot d^{-1}$) and 7.4 g $kg^{-1} \cdot d^{-1}$ (6.3~8.7 g $kg^{-1} \cdot d^{-1}$). Among the three compositions tested, water extraction was not able to fulfil LD_{50} of 30 g $kg^{-1} \cdot d^{-1}$. This was found to be equivalent to 76.92 times of a 70 kg adult daily dried herb consumption (R. R. Li, Yang, Ding, Qin, & Li, 2012). In CHM, herbal decoction in water extract is regarded as the golden standard for consuming and preparing CHM. The strategy in pairing herbs or formulating herbs which involve a toxic herb in CM is based on the principle of mutual counteraction (Xiang Wei) where the toxicity of herbs are reduced or neutralised when paired with another herb. In the case of Xi Xin, pairing with Dan Shen *(Salviae Miltorrhizae Radix et Rhizoma*), Chi Shao (*Paeoniae Radix Rubra*) or Wu Wei Zi (*Schisandrae Chinensis*) is recommended (Sionneau, 1997). Depending on the syndromes, these herbs have longed been used to supress the toxicity. In addition, boiling of decoction for Xi Xin requires 45 minutes to totally eliminate the toxic substances (C. Chen et al., 2009). Therefore, the water extraction method confirmed the toxicity of Xi Xin was negligible to impart nephropathy. In spite of the positive evidence that low dosages of Xi Xin and Cang Er Zi may not present acute toxicity, it is highly encouraged that caution and drug vigilance should be exercised.

6.8. Discussion

The bioactive chemical components of natural products are essential building blocks for novel drug development. For natural products to be defined as therapeutic natural products, four broad acceptable definitions include the following: First, it is an unregulated organisms or natural materials; second, a FDA-regulated, unmodified natural materials or compounds; third, a semisynthetic compound – a naturally occurring compound that has been chemically modified and fourth; a purely synthetic medicinal compound inspired by a natural compound (Patridge, Gareiss, Kinch, & Hoyer, 2016).

By chemical modification, biological and chemical engineering, the naturally occurring bioactive compounds can be improved by these methods to produce superior drugs to target chronic diseases more effectively.

The review of the five top herbs commonly used clearly underscores the pharmacodynamics and the diversity of their bioactive chemical compounds on molecular mechanisms, multiple pathways and its regulatory indications. The reception of CHMs for medicinal purposes has been instilled by fearmongering stirred by a faction of scientific community or owing to ignorance. Yet, to date, new molecular entities that were approved by FDA derivatives from natural products: 44% from mammals with the primary species of origin being (in order of frequency) bovine, porcine, equine, canine and human, 25% from plant, 16% from bacteria, 12% from fungi and 30% from bacteria (Patridge et al., 2016). In fact, at least 35 different natural-product based new molecular entities that target opioid or neurotransmitter receptors accounted 94% derived from plants (Patridge et al., 2016).

The outcomes of this review unveil many other potentiated pharmacological effects of CHM used for the management of AR such as anti-inflammation and anti-allergic, anti-nociceptive and analgesia, anti-oxidative and anti-proliferative, immunoregulatory and immunostimulatory for different biological systems of disease. Toxicological evidence revealed both Cang Er Zi and Xi Xin are toxic in regards to their levels of toxicities and their effects on the health system. Exposure of AA-I induced mutated adenines in the genome associated with A→T transversion at 5′AG (acceptor) splice site accounts for 30%, and 20% represent all other mutations (Grollman, 2013). These mutations represent a failure of DNA to repair its strand and account for the persistence of lesions in human tissues. Toxicities induced by AA-I are known as AA nephropathy. Given the use of Xi Xin and Cang Er Zi, many of cases of AA nephropathy are due to linear dose-response relationship established between consumption of herbal remedies

(Grollman, 2013) and risk developing chronic renal disease, upper urothelial carcinoma, hepatocellular necrosis and liver disease (Grollman, 2013; Yu et al., 2013).

To date, Taiwan has the highest recorded renal-pelvis-urethra AA-I induced mutagenesis owing to use of *Aristolochia* herbs which accounts for one third of the population (Grollman, 2013). The main reason for the increase of the incidence of AA-I is iatrogenic, where CM practitioners prescribe *Aristolochia* herbs with little or no knowledge of restrictions and dose-related requirements. It is important that ongoing education on the molecular toxic effects of AA-I herbs be reinforced to CM practitioners. At the grassroots level, bodies of authorities in relation to CM practice need to exercise more stringent surveillance of herbal dispensary, even though a restriction on the use of Xi Xin is in place in Australia. All species of *Aristolochia* are prohibited for supply, sale or use in therapeutic goods in Australia under the Standard for the Uniform Scheduling of Drugs and Poisons (Therapeutic Goods Administration, 2001). However, *Aristolochia* species especially Xi Xin may still be presented in other CM herbal-based products for sale in Australia, vigilance has to be exercised.

Although Cang Er Zi is not restricted, it is known for its toxicities yet it has beneficial effects in AR. Informed usage of this herb has to be reinforced to prevent unforeseen endemic AA-I susceptibilities in patients seeking CM.

With the well-established understanding of the usage of herbs, sustained efforts in research of herbs for drug development and education on its application in clinical practice can expand the drug resources for treatment of diseases.

Chapter 7 Results III – Review of CM classic literature

This chapter reports the outcomes from the principal component and hierarchical cluster analyses of the main classical texts for AR-like signs and symptoms and identifies the commonly used herbs in the classics.

7.1. Results of literature search

A total of 1,687 articles were searched from ZHYD and ZGBQS and 294 articles were included in the review which identified 163 herbs were used in ancient times for the management of AR (Figure 50).

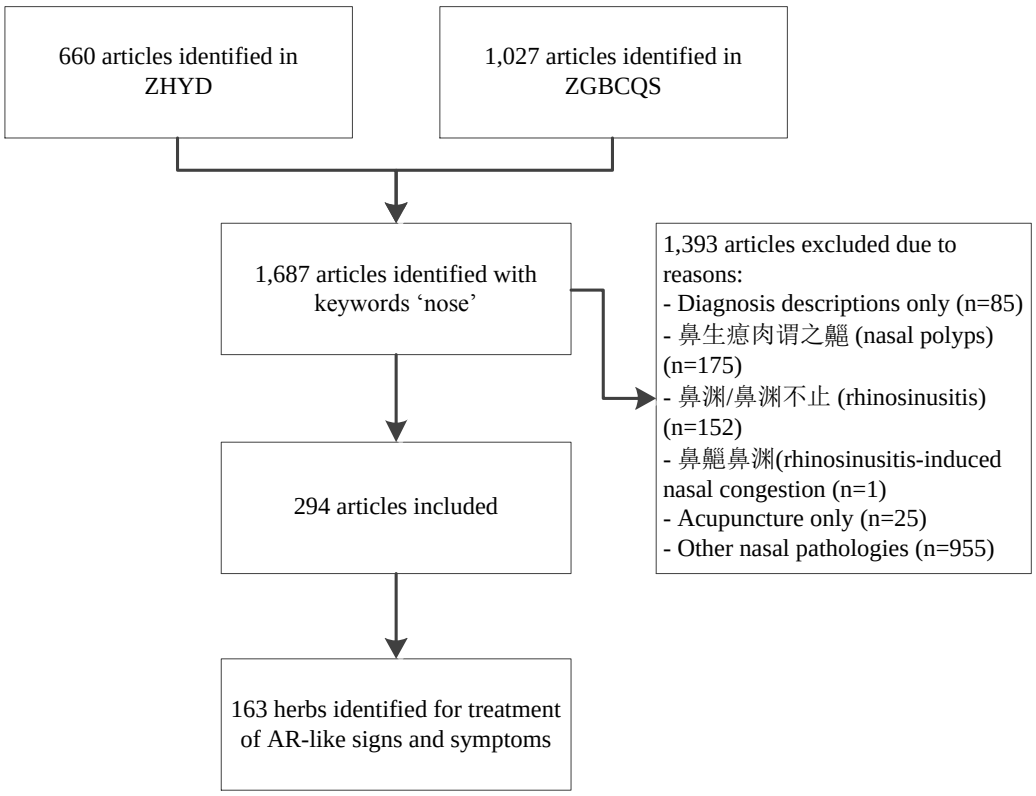


Figure 50. Search process for ZHYD and ZGBCQS

7.2. Descriptions of selected classical texts

The following table is a summary of classical texts with relevance to AR-like signs and symptoms in ZGBCQS (Table 19).

Table 19. Summary of classical texts in ZGBCQS containing AR-like signs and symptoms

Volumes	No. of Books	Names of books and sections	Periods
2	7	神农本草经（马继兴辑本） Shennong's Classics of Materia Medica	5th century
		神农本经（卢复辑本） Compendium of Shennong's Classics of Materia Medica	17th century
		本草经 Materia Medica	17th century
		神农本草经（孙星衍、孙冯翼辑本） Shennong's Classics of Materia Medica	9th century
		神农本草经（狩谷棭斋辑本） Shennong's Classics of Materia Medica	9th century
		神农本草经（森立之辑本） Shennong's Classics of Materia Medica	9th century
		神农本草（王仁俊辑本） Shennong's Classics of Materia Medica	9th century
3	3	注解神农本草经 Annotations of Shennong's Classics of Materia Medica	19th to 20th century
		神农本经（姜国伊辑本） Shennong's Classics of Materia Medica (American Edition)	19th century
		神农本经校注 Notes on Shennong's Classics	20th century
5	5	本草经集注 Reconstituted Annotations of Materia Medica	No date
6	12	新修本草 Newly Revised Materia Medica (Tang Materia Medica)	No date
		食疗本草 Dietetic Materia Medica	7th century to 8th century
		何首乌录 Records of *Polygoni Multiflori Radix*	8th century to 12th century
		石药尔雅 Minerology in Medicine	8th century to 12th century
		食医心鉴 Reflections on Food for Medicine	8th century to 12th century
		药谱 Drug Register	8th century to 12th century
7	1	海药本草 Overseas Materia Medica	5th century to 11th century
7	1	经史证类备急本草 Annals of Exigent Syndromes Materia Medica	5th century

Volumes	No. of Books	Names of books and sections	Periods
8	1	经史证类备急本草 Annals of Exigent Syndromes Materia Medica	11th century
9 -11	3	经史证类大观本 Annals of Syndromic Catalogue of Materia Medica	12th century
11-13	1	重修政和经史证类备用本草 Recompilations of Annals of Exigent Syndromes Materia Medica	12th century
13-14	1	绍兴校定经史证类备急本草（龙谷大学本） Shaoxing Materia Medica	13th century
14-15	1	绍兴校定经史证类备急本草画卷 Shaoxing Materia Medica with Pictorial Inserts	12th century
15-16	3	绍兴校定经史证类备急本草（神古克桢本） Shaoxing Materia Medica	No date
		本草衍义 Elucidations of Materia Medica	19th century
		图经本草药性总论 Comprehensive Blueprints of Materia Medica	12th century
18	1	图经衍义本草 Elucidations of Materia Medica Blueprints	13th century
19	2	图经衍义本草 Comprehensive Blueprints of Materia Medica	13th century
		类编图经集注衍义本草 Complete Blueprints Assortments of Materia Medica	No date
22	7	珍珠囊 Pearls of Wisdom in Gastrointestinal Doctrine	No date
		汤液本草 Doctrines of Herbal Decoction	13th to 14th century
		本草元命苞 Materia Medica for the Preservation of Life	13th to 14th century
		本草衍义补遗 Elucidations on the Addendum to the Complete Materia Medica	14th century
		日用本草（嘉靖四年刻本） Conventional use of Materia Medica	14th century
		日用本草（万历四十八年刻本） Conventional use of Materia Medica	15th century
		饮膳正要 Dietary Nutrition	15th century
24	3	滇南草本（务本堂本） Southern Yunnan Materia Medica	15th century
		滇南本草图说 Southern Yunnan Herbal Picture Book	15th century
		滇南本草（云南丛书本） Southern Yunnan Materia Medica	15th century
24	1	滇南本草（云南刻本） Southern Yunnan Materia Medica	15th century
25	4	滇南本草（云南刻本） Southern Yunnan Materia Medica	15th century

Volumes	No. of Books	Names of books and sections	Periods
		滇南本草(沐忠本) Southern Yunnan Materia Medica	15th century
		药性赋 Herbal Properties	15th century
		本草集要 Notes on Materia Medica	15th century
26	3	新编注解药性赋 Commentary on Herbal Properties	15th century
		本草约言 Covenant of Herbal medicine	16th century
		食物本草（胡文焕精抄本） Food as Medicine	14th to 17th century
28-37	1	(御製本草品彙精要)本草品彙精要（罗马本） Herbal Essentials Collection	16th century
38-41	2	本草纲目（金陵本） Compendium of Materia Medica	16th century
41-47	1	本草纲目（武林本） Compendium of Materia Medica	16th century
48-52	1	本草纲目（味古斋本） Compendium of Materia Medica	16th century
53-54	1	神农本经会通 Mutual Annotation of Shennong's Classics of Materia Medica	15th century
54	3	鼎刻京板太医院校正分类青囊药性赋 Correction of the classification of Chinese Materia Medica in Imperial Academy of Hospital in Beijing	16th century
		医方药性合编 Edition of Medical Prescriptions	16th century
		食品集 Food Collections	16th century
55	5	食鑑本草 Materia Medica for Dietary Therapy	16th century
		体仁彙编·十二经络脏腑病情药性 Benevolence practice – Interactions of medicine and 12 meridians and Zang Fu diseases	16th century
		新刻药证类明 Illuminations on novel drugs	16th century
		南产志 Records of Chinese Materia Medica produced in Southern China	16th century
		太医院补遗本草歌诀雷公炮製 Addendum to University Hospital on Decoction of Processed Herbal Medicine	16th century
56	1	药性粗评 Debate on Herbal Medicine	16th century
56	1	本草发明 Invention of Materia Medica	16th century
58	2	新刻太乙仙製本草药性大全 Compendium of Mystical Efficacy of Herbal Medicine	17th century
		饮馔服食谱 Recipes of Foods and Beverages	16th century

Volumes	No. of Books	Names of books and sections	Periods
59	3	本草定衡 Revaluation of Materia Medica	16th century
		万病回春·药性歌 Rhymes on Herbal Efficacy -Rejuvenation from Thousand Diseases	16th century
		伤寒论条辨·本草钞 Treatise on Shang Han Lun Materia Medica	16th century
60	1	本草选 Herbal Medicine Selection	17th century
61	2	药鑑 / 药鉴 Governance on Medicine	17th century
		本草原始（李中立绘图本） Origins of Herbal Medicine	17th century
62	2	本草原始（永怀堂刻本） Origins of Herbal Medicine	17th century
		炮炙大法 Art of Processed Medicine	17th century
63	3	本草真诠 Original Exposition of Herbal Medicine	17th century
		食物辑要 Edition on Foods	17th century
		芷园臆草题药 Impression on Chinese Materia Medica by Zhi Yuan	17th century
64	1	本草彙言/本草汇言 Discourse on Herbal Medicine	17th century
67	3	食物本草 Herbal Foods	17th century
		野菜博录 Records of Wild Plants	17th century
		景岳全书·本草正 Complete Works of Jingyue	17th century
68	4	珍珠囊指掌补遗药性赋 Pearls of Wisdom Addendum to Fu Herbs	17th century
		镌补雷公炮製药性解 Lei’s Supplementary Exposition on Processed Herbs	17th century
		镌补雷公炮製药性解 Lei’s Supplementary Exposition on Processed Herbs	17th century
		养生要括 Inclusions on Health	17th century
69-70	1	神农本草经疏 Notes on Shennong’s Classics of Materia Medica	17th century
71	1	分部本草妙用 Sections on Mystical Use of Herbs	17th century
71	1	医宗必读·本草征要 Compulsory Clinical Readings on Herbal Evidence	17th century
72-74	3	食物本草（姚可成辑本） Herbal Foods	17th century
		明医选要·药性诗诀 Choice of Clinical Fame · Poetry on Herbs Efficacy	17th century

Volumes	No. of Books	Names of books and sections	Periods
		山公医旨食物类 Top Medical Advice on Foods for Medicine	17th century
76	3	药镜 Reflections on Medicine	17th century
		药品化义 Drugs of Justice	17th century
		新锲药性会元 Potency of New Element	15th century
78	3	本草纂要 Medicinal Compilations	16th century
		仁寿堂药镜 Reflections on Compassion and Longevity in Herbal Medicine	17th century
		新刊校正李东垣官板药性大全 New Editions on Corrections of Medicinal Properties Compilation by Li Dong Yuan	17th century
79-83	4	本草品彙精要（大塚本） Herbal Collection Essentials	16th century
		本草歌括（八卷本） Herbal Rhymes	14th century
		本草歌括（二卷本） Materia Medica Rhymes	14th century
		本草发挥 Efficacy of Herbal Medicine	15th century
84	3	本草歌括（八卷本） Herbal Rhymes	16th century
		本草纲目类纂必读 Essential Proses on the Compendium of Materia Medica	17th century
		食宪鸿秘 Secrets of Food and Constitution	18th century
85-86	2	本草汇 Transmissions on Herbal Medicine	17th century
		寿世秘典 Secret Code of Longevity	17th century
87	2	本草彙笺 Annotations of Materia Medica	17th century
		经方衍义 Elucidations of Jing Fang	17th century
88	1	本草洞诠 Complete Exposition on Materia Medica	17th century
89-91	1	本草述 Narrations on Materia Medica	17th century
93	1	本草纲目必读 Compulsory readings of Compendium of Materia Medica	17th century
95	4	本草通玄 Tong Xuan Materia Medica	17th century
		农经酌雅 Discretionary Farmer’s Treatise	17th century
		本草崇原 Origins of Herbal Medicine	17th century

Volumes	No. of Books	Names of books and sections	Periods
		生草药性备要 Preparation of Herbal Medicine	17th century
96	2	药性纂要 Compilations on the Efficacy of Medicine	17th century
		药品辨义 Debate on Quality of Medicine	17th century
98	3	医学启蒙彙编 Compilations on the Enlightenments of Medicine	16th century
		食物本草会纂 Compilations of Food as Medicine	16th century
		颐生秘旨 Secrets of Nourishing Life	18th century
99	1	山居本草 Mountain Herbs	17th century
101	2	本经逢原 Doctrine of Origin	17th century
		药理近考 Test on Pharmacology	17th century
102	3	杂症痘疹药性合参 Indications of Small Pox and Herbal Medicine	17th century
		得宜本草分类 The Legitimate Herbal Medicine	18th century
		长沙药解 Changsha Exposition on Medicine	18th century
103	3	夕庵读本草快编 Fast Composition of Chinese Materia Medica by Xi'an	17th century
		绛雪园得宜本草 Jiang Xue Legitimate Herbal Medicine	18th century
		医林纂要探源 Original Compilation of Medicine	18th century
105	2	药性通考 Biographical Notes on Medicinal Efficacy	18th century
		要药分剂 Analysis of Medicine	18th century
108	1	要药分剂补正 Commendable Analysis of Medicine	19th century
108	1	食物小录 Food Records	18th century
110	2	法古录 Following Ancient Records	18th century
		质问本草 Questions on Materia Medica	18th century
111	1	脈药联珠药性食物考 Criticism on Apllicaiotn of Pulse, Syndrome and Chinese Materia Medica	18th century
113	1	毛诗名物图说 Illustration of Chinese Materia Medica	18th century
114	2	增补药性雷公炮製 Supplementary to Efficacy of Processed Medicine	19th century

Volumes	No. of Books	Names of books and sections	Periods
		本草述录 Records of Materia Medica	19th century
115	1	本草纲目拾遗 Corrections of Compendium of Materia Medica	18th century
117	2	本草经疏辑要 Collections of Monastic Herbs	19th century
		本草正义 Merits of Herbal Medicine	19th century
119	5	本草纂要稿 Draft Complication of Herbs	19th century
		四言药赋 Medicinal Ode in Four Character Verse	19th century
		类经证治本草 Category of Herbal Treatment	19th century
		简易草药草方图说 Simplified Pictures of Herbal Medicine	19th century
		药达 Attainment of Chinese Materia Medica	19th century
121	1	本草述钩元 Origin and Link of Herbal Medicine	19th century
124	2	本经续疏·本经序疏要 Disseminations of Treatise	19th century
		济荒必备 The Necessity of Economy	19th century
125	1	本草求真 Truths of Materia Medica	18th century
126	2	药性集要便读 Volumes of Potency of Medicine	19th century
		锦囊药性赋 Tips on Potency of Fu Medicine	19th century
131	1	植物名实图考长编 Pictogram of Plants	19th century
135	1	务中药性 Works of Chinese Medicine	19th century
135	1	天宝本草 Heavenly Treasure Herbal Medicine	19th century
136	4	神农本草经赞 Merits of Shennong’s Classics of Materia Medica	19th century
		药性摘录 Records of Herbal Extracts	19th century
		本草省常 Common herbs	19th century
		随息居饮食谱 Increasing Spectrum of Home Diet	19th century
137	1	本草经考注 Notes on Materia Medica	19th century
138	1	本草再新 Revival of Materia Medica	19th century
139	4	本草汇编	19th century

Volumes	No. of Books	Names of books and sections	Periods
		Collection of Materia Medica	
		本草明览 Overview on Herbs	19th century
		药性蒙求 Annotations on Herbal Efficacy	19th century
		本草汇纂 Discourse on Herbal Medicine	19th century
142	1	本草纲目易知录 Understandings of Compendium of Materia Medica	19th century
143	3	本草正论 Discussions on Materia Medica	19th century
		稽古摘要 Summary of the Practice	19th century
		本草简明图说 Facsimile of Materia medica	19th century
144	4	草木便方 Benefit of Herbal Medicine	19th century
		药要便蒙新编 Overview of Herbs and its Usage	19th century
		本草害利 Effects of Herbs	19th century
		本草衍句 Disseminations on the Materia Medica	19th century
146	3	虫荟 Entomology	19th century
		本草问答 Questions and Answers on Herbs	19th century
		本草韻语 Rhymes on Herbal Medicine	19th century
148	1	分类草药性 Studies on Types of Herbal Efficacy	20th century
148	10	每日食物却病考 Eliminating Disease Utilising Daily Foods	20th century
		分类草药性 Studies on Types of Herbal Efficacy	20th century
		本草（清抄本） Materia Medica	20th century
		简明药性 Illuminating Herbal Efficacy	20th century
		九龙虫治病方 Beetles and Thousands Cures	20th century
		本草类考 Types of Herbs	20th century
		本草分经（张节著本） Doctrines on Materia Medica	20th century
		药性提要歌诀 Rhymes on Herbal Efficacy	20th century
		药性要略 Debate on Herbal Efficacy	20th century

Volumes	No. of Books	Names of books and sections	Periods
		本草知要 Fundamentals on Materia Medica	20th century
149	3	本草释名类聚 Names of Herbs	20th century
		本草须知 Fundamental Knowledge on Herbal Medicine	20th century
		本草分队 Types of Herbs	20th century
150	6	本草二十四品 24 Types of Herbs	20th century
		药谱字类 Writings on Medicinal Herbs	20th century
		本草（程龄源著本） Materia Medica	20th century
		备用药物 The Necessary Medicine	20th century
		药性新编 New Edition on the Efficacy of Herbal Efficacy	20th century
		四言药性分类精要 Synopsis on Herbal Efficacy	20th century
151	4	神农本草经抄今注 Annotations to the Shennong's Classics of Materia Medica	20th century
		本草约编（清抄本） Herbal Series	20th century
		用药法程 Methods of Using Processed Herbs	20th century
		药性钞 Summary on Herbal Efficacy	20th century
151	3	药性探源 The Origin of Herbal Efficacy	20th century
		本草歌括详注 Rhymes on Herbal Medicine	20th century
		药性骊珠 Pearls of Wisdom of Herbal efficacy	20th century
153	1	本草十三家註 Thirteen Texts on Herbs	20th century
155	3	辞典本草 Encyclopaedia on Herbs	20th century
		食物治病新书 New Edition to Food as Medicine	20th century
		药名杂钞 Nomenclature of Herbs	20th century
156	3	神农本草经注论 Discussions on Shennong's Classics of Materia Medica	20th century
		党参新研究 New Study on Dang Shen	20th century
		药性精髓 Essence of Herbs Efficacy	20th century

Volumes	No. of Books	Names of books and sections	Periods
157	3	本草疏证 Rectifications in Materia Medica	20th century
		杂类药性书 Text on Varied Herbal Efficacies	20th century
		研药指南 Manual of Herbal Exposition	20th century
158	1	本草求原 Origin of Materia Medica	19th century
159	4	药性选要 Choosing the Right Herbs for Efficacious Outcome	20th century
		药名诗 Poetry on the Nomenclature of Herbs	19th century
		中国新本草图誌 China Latest Herbal Facsimile	20th century
		药物出产辨 Discussions on Manufacturing Process of Drugs	20th century
160	3	岭南采药录 Understandings the Use of Herbal Medicine	20th century
		中国实用药物 China Clinical Practice In Herbs	20th century
		药物图考 Facsimiles of Herbs	20th century
161	2	分类饮片新参 Types of Patent Medicine	20th century
		国药诠证 The Heritage of Herbs in China	20th century
162	3	马王堆医书五种 Five Types of Ma Wang Dui Clinical Text	3rd century
		武威汉代医简 Wuwei Han Dynasty Clinical Text	1st century
		敦煌出土不知名医方二十三种 Twenty-three Unknown Buddhist Herbal Formulae	7th century to 10th century
163	2	金匮要略方论 Discussions on Synopsis of Prescriptions of the Golden Chamber	1st century
		肘后备急方 Use of Emergency Herbal Formulae	4th century
164	1	备急千金要方 Treasures in Emergency Formulae	7th century

There are 740 volumes in ZGBCQS containing CHMs. Among them, a total of 129 out of 164 volumes were singled out to contain information related to AR-like signs and symptoms.

AR-like signs and symptoms classified were found under several genres in ZHYD, with the titles of the books classified under Materia Medica 本草类; medical doctrines genres 医经类; prescriptions genres 方书类; Comprehensive Materia Medica 综合本草; 综合方书 comprehensive collections of formulae books 综合方书; comprehensive medical genres 综合医书类; 温病类 warm diseases 温病类; 伤寒金匮 cold damage and Jin Gui 伤寒金匮; comprehensive medicine 综合医书类; clinical and specialisations genres 临证各科类; diet and health preservation 养生食疗外治类; clinical discussions and cases 医论医案类; Chinese medicine dictionary 中医辞典. Out of 1,156 books in ZHYD, 94 books were found to contain information related to AR-like signs and symptoms (Table 20).

Table 20. Summary of classical books in ZHYD containing AR-like signs and symptoms

Genres	**No. of books**	**Names of books and sections**	**Periods**
医经类 **Medical Doctrines**	1	黄帝素问宣明论方 Enlightened Discussion of Suwen in the Emperor's Inner Canon	3rd to 5th century
本草类 **Materia Medica** **综合本草** **Comprehensive Materia Medica**	13	本草经集注 Annotations of Materia Medica	6th century
		新修本草 Newly Revised Materia Medica	7th century
		本草图经 Materia Medica Facsimiles	7th century
		名医别录 Alternative records for practice	11th century
		证类本草 Syndromes of Materia Medica	3rd to 5th century
		本草品汇精要 Essential Herbal Collections	16th century
		本草纲目 Compendium of Materia Medica	16th century
		本草征要 Materia Medica Evidence	16th century
		本草易读 Comprehensible Materia Medica	11th century

Genres	No. of books	Names of books and sections	Periods
		本草纲目拾遗 Supplementary Texts to Compendium of Materia Medica	18th century
		本草崇原 Origin of Materia Medica	17th century
		炮炙大法 Comprehensive Handbook on the Processing of Drugs	16th century
		本草详节 Interpretations of the Materia Medica	17th century
方书类 **Prescriptions genres** **综合方书** **Comprehensive collections of formulae books**	3	太平圣惠方 Peaceful Holy Benevolent Prescriptions	10th century
		孙真人海上方 Sage's Kong Formulae of the Sea	7th to 10th century
		华佗神方 Hua Tuo's Divine Formulae	16th century
方书类 **Prescriptions genres** **综合方书** **Comprehensive collections of formulae books**	17	小品方 Formulary of Trifles	16th century
		苏沈良方 Su Shen Formulae	5th century
		圣济总录 Sacred Compilations of Disseminations	10th to 12th century
		鸡峰普济方 Universal Capstone of Formulae	12th century
		普济本事方 Universal Formulae	10th to 12th century
		妇人大全良方 Compendium of Prenatal Formulae	13th century
		仁斋直指方论（附补遗） Addendum to Pool of Benevolence Formulae	13th century
		严氏济生方 Yan Shi Ji Sheng Formulae	13th century
		瑞竹堂经验 Tested Formulae of Ruizhi Hall	13th century
		御药院方 Royal Hospital Medicine	14th century
		世医得效方 Effective Herbal Formulae in Medicine	13th century
		是斋百一选方 Selected Formulae by Wang Qiu Yuan	13th to 14th century
		传信适用方 Transmissions in Formulae	12th century
		活人事证方后集 Testimony of the Living Formulae	12th century
		卫生易简方 Easy Formulae for Health	10th to 13th century

Genres	No. of books	Names of books and sections	Periods
		普济方 Universal Formulae	15th century
		奇效良方 Miraculous Formulae	14th to 17th century
方书类 **Prescriptions genres** **综合方书** **Comprehensive collections of formulae books**	16	医方考 Medicinal Formulae	15th century
		仁术便览 Benevolence Handbook	16th century
		鲁府禁方 House of Fu Forbidden Formulae	16th century
		祖剂 Ancestral Decoctions	16th century
		普济方 Universal Formulae	12th to 14th century
		证治准绳·类方 Standards of Proven Formulae	17th century
		扶寿精方 Formulae for Supporting Longevity	17th century
		医方选要 Choice Herbal Medicine	16th century
		万氏家抄济世良方 Wan's Ancestral Formulae	15th century
		种福堂公选良方 Hall of Zhong Fu Choice Formulae	16th century
		成方切用 Explanations on Use of Patent Medicine	18th century
		太医院秘藏膏丹丸散方剂 Secret Plaster, Pill and Powder Prescriptions in Imperial Academy of Hospital	17th to 18th century
		古方汇精 Enlightened Discussion of Ancient Formulae	19th century
		喻选古方试验 Experienced Selections of Ancient Formulae	19th century
		不知医必要 Fundamentals Knowledge of Medicine	19th century
		医略抄 Discussions on Medicine	18th century
方书类 **Prescriptions genres** **综合方书** **Comprehensive collections of formulae books**	9	历验再寿编 Essay on Rejuvenation through the Ages	20th century
		救生集 Chapter on Rescue Medicine	21th century
		秘方集验 Classified Formulae	17th century

Genres	No. of books	Names of books and sections	Periods
		医方集解 Medicinal Formulae	17th century
		上部病 Upper Body Disease	No date
		续名家方选 Famous Formulae	19th century
		外治寿世方 External Herbal Formulae Treatment through the Ages	17th to 20th century
		单方验方.回 生 集 Single Formulae	No date
		温病通论 Discussions on Warm Diseases	No date
温病类 **Warm diseases genre**	1	伤寒论 Treatise on Cold Damage Diseases	18th century
伤寒金匮类 **Cold Damage and Golden Chamber genres** **综合医书类** **Comprehensive medical genres**	6	诸病源候论 Discussions of Pathogenesis of Diseases	7th century
		周慎斋遗书 Testimony of Zhou Zhen	13th to 14th century
		证治汇补 Revision of Standards	17th century
		医方集宜 Formulae Edition	14th to 17th century
		丹溪治法心要 Danxi's Experiential Therapy	13th to 14th century
		寿世保元 Longevity and Life Preservation	17th century
伤寒金匮类 **Cold Damage and Golden Chamber genres** **综合医书类** **Comprehensive medical genres**	10	古今医统大全 Complete Compendium of Medical Works, Ancient and Modern	16th century
		万病回春 Recovery from All Ailments	16th century
		明医杂著 Famous Clinical Practice Essays	17th century
		丹溪手镜 Danxi's Handbook of Reflections	13th to 14th century
		张氏医通 Zhang's Medical Canon	17th century
		医学心悟 Thoughts on Medical Practice	18th century
		冯氏锦囊秘录 Feng's Records of Secret Tips	1tth to 18th century
		医学纲目 Compendium of Medical Practice	14th to 18th century
		医学研悦 Exposition on Medicine	14th to 17th century

Genres	No. of books	Names of books and sections	Periods
		内科通论 Discussions on Internal Medicine	19th century
临证各科类 **Clinical and specialisations genres**	6	儿科通论 Discussion on Pediatrics Medicine	17th to 20th century
		慈幼便览 Charitable Guide	No date
		原幼心法 Therapeutic Methods for Paediatrics	14th to 17th century
		儿科专论 Discourse on Paediatrics	No date
		外科通论 Discussions on External Medicine	19th century
		内科通论 Discussion on Internal Medicine	14th to 17th century
养生食疗外治类 **Diet and health Preservation genres**	1	巢氏病源补养宣导法 Chao's Tonifying and Guiding Methods for Diseases	No date
养生食疗外治类 **Diet and health preservation genres**	4	养生导引秘籍 Secrets to Health	14th to 17th century
		养生导引法 Art to Good Health	14th to 17th century
		急救广生集 Chapters on Emergency Medicine	19th century
		临证指南医案 Manual on Clinical Cases	18th century
医论医案类 **Clinical discussions and cases**	4	旌孝堂医案 Manifestations on the Clinical Cases	No date
		临症经应录 Records of Clinical Diagnosis	17th to 20th century
		沈菊人医案 Clinical Cases by Shen Juren	17th to 20th century
		叶天士曹仁伯何元长医案 Yetianshi and Caorenbo Clinical Diagnosis	17th to 20th century
中医辞典 **CM Encyclopaedia**	2	专科专病中成药 Patent Medicine for Specialty Medicine	17th to 20th century
		外用剂 External Medicinal Decoction	No date

7.3. Scoring outcomes of classical herbal formulae/herbs

A total of 163 herbs were identified from the combined sources of ZHYD and ZGBCQS, were used for the management of AR-like signs and symptoms in ancient times. Ten animal products, three minerals and two bodily excretory products (sediment of human urine and horse urine) were used for the management of AR-like signs and symptoms. Animal products for AR treatment consist of scorpions (Figure 51), dung beetles, earthworms (Figure 52), goats' lungs (Figure 53) and buffaloes' horns (Figure 54) to treat nasal congestion, a late phase symptom manifestation of AR.

Figure 51. Scorpions (Photograph by Kreiner, J.)

Figure 52. Earthworms (Photograph by Kreiner, J.)

Figure 53. Goats' lungs (X. P. Gu 2016)

Figure 54. Buffaloes' horns (China Medicinal Herb Suppliers, 2010)

Many natural products were used to treat nasal congestion. Yellow-coloured canine meat and in particular yellow canine skull ash were used. Canine meat was prescribed to address nasal congestion arising from deficiency of the Spleen's transport and transformation as well Kidney Yang deficiency. The classical texts described canine meat could invigorate the Qi and strengthen the Spleen and Kidney. To relieve nasal blockage, canine skull ash was administered by blowing into the nostrils to unblock the orifices. Three minerals Zhu Sha Liu Huang and Shi Lü were used to treat nasal congestion by means of blowing through the nostrils. The bodily secretory products include sediments of human urine (Figure 55) and horse urine (no picture

are available) were used to treat congested nose with runny discharge. Residues from plant soot scraped from a boiler (Figure 56) were also featured as one of the remedies for nasal congestion.

Figure 55. Sediments of human urine (Baidu wiki, 2015)

Figure 56. Plant soot residues scraped from boiler (Bao & Qi 2015)

Bi Chong Shui (nasal irrigation fluid) was described to be used for nasal congestion and the content for this fluid was noted as unknown as it was a foreign product introduced from the West. The passage even described how the product should be administered for the type of condition associated with it (Figure 57).

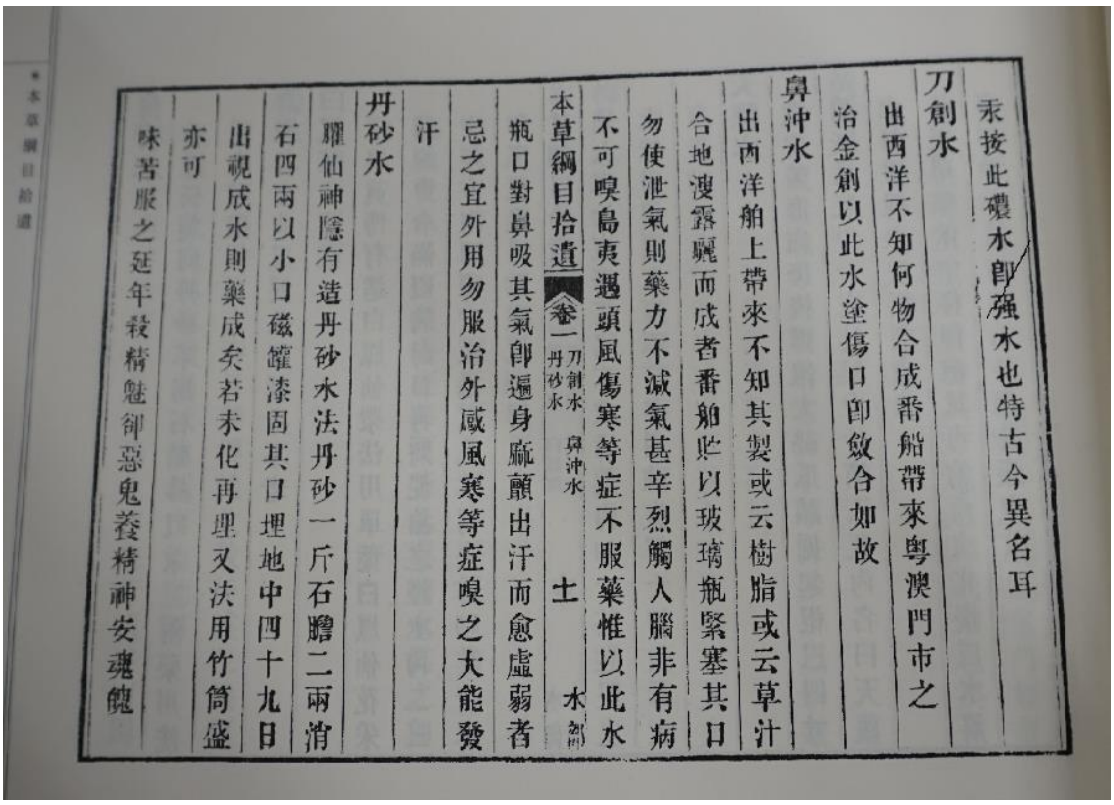


Figure 57. Passage extract on nasal irrigation fluid (Bi Chong Shui) (Photograph by Kreiner, J.)

A combined outcome of the systematic scoring in combined texts of ZGBCQS and ZHYD produced outcome on top five herbs used in ancient CM clinical practice were Xi Xin (132 citations), Xin Yi (70 citations), Bai Zhi (35 citations), Bo He (31 citations) and Gua Di (31 citations) (Table 21).

Table 21. Combined frequency and ranking of herbs from ZHYD and ZGBCQS

Herbs	Frequency of Citations	Ranking
Xi Xin (*Asari Radix et Rhizoma*)	132	1
Xin Yi (*Magnoliae Flos*)	70	2
Bai Zhi (*Angelicae Dahuricae Radix*)	35	3
Bo He (*Menthae Haplocalycis Herba*)	31	4
Gua Di (*Pedicellus Trichosanthis*)	31	4
Gan Cao (*Glycyrrhizae Radix et Rhizoma*)	30	5
Chuan Xiong (*Ligustici Rhizoma***)**	28	6
Fang Feng **(***Saposhnikoviae Radix***)**	28	6
Huang Qi (*Astragali Radix*)	27	7
Cang Er Zi **(***Xanthi Fructus*)	25	8
Sheng Jiang (*Zingiberis Rhizoma Recens*)	25	8
Fu Zi (*Aconiti Lateralis Radix Preparata*)	22	9
Tong Cao (*Tetrapanacis Medulla*)	22	9
Jie Geng (*Platycodonis Radix*)	18	10
Ren Shen (*Ginseng Radix*)	18	10
Nan Xing (*Arisaematis Rhizoma*)	17	11
Cong Bai (*Bulbus Allii Fistulosi*)	16	12
Gan Jiang (*Zingiberis Rhizoma*)	16	12
Qiang Huo (*Notopterygii Rhizoma et Radix*)	16	12
Mu Tong (*Akebiae Caulis*)	15	13
Bai Zhu (*Atractylodis Macrocephalae Rhizoma*)	14	14
Pi Ba (*Piper Longum*)	14	14
Xiong Huang (*Realgar*)	14	14
Chang Pu (*Rhizoma Acori Tatarinowii Rhizoma*)	13	15
Ji Li (*Tribuli Fructus*)	12	16
Gui (*Cinnamom Ramulus*)	11	17
Jing Jie (*Schizonepetae Herba*)	11	17
Ju Hua (*Chysanthemi Flos*)	11	17
Si Gua Teng Jin Geng (*Pedicellis Luffa Retinervus*)	11	17
Zhi Zi (*Gardeniae Fructus*)	11	17

7.4. Principal component analysis of herbs

The PCA emphasises on the correlation of variables (AR-like signs and symptoms) to the herbs used in the management of AR. Squared loadings in the PCA define the correlation between a component and a variable. Loadings impart information on the proportion of variance of the herbs analysed while the eigenvalues summarise the amount of information (inertia) in the PCA dimension. Inertia refers to the total variance of a dataset, which marks the dimension or distance of the correlation matrix and it also denotes the importance of the component (Abdi & Williams, 2010). The sum of squared coefficients of correlations between a variable (herb) and all the components is equal to eigenvalue of 1. When the coefficient of a component is closer to the centre of the plot, eigenvalue is generally less than the value of 1. Therefore this means the component is less important. Eigenvalue greater than 1 is considered more important. The loadings essentially are positioned within the circle of correlations, this correlation is determined by the loadings on component space (Abdi & Williams, 2010).

A total of 163 herbs were analysed against 11 AR-like signs and symptoms cited in the classical literature: sneeze, congested nose with runny nose discharge, sinusitis, nasal congestion, itchy nose, allergic rhinitis, postnasal drip, listlessness, headache with eye pain, pain the nose and red nose. These made up the 11 components used to evaluate the effects of the herbs. Only three components namely, Component 1 (nasal congestion), Component 2 (congested nose with runny nose discharge) and Component 3 (sinusitis); were identified with eigenvalues of more than 1, which are 5.357, 1.235 and 1.029, respectively. The variance of the loadings for Components 1, 2 and 3 were 48%, 11 % and 9%, respectively. Although Component 3 eigenvalue is more than 1, its inertia accounts for only 9.4%. Together both Components 1 and 2 accounted for more than 60% of the variance for the loadings (Table 22). Therefore, the herbs with attributes of Components 1 and 2 are likely to imply better effects in the treatment of AR-

like signs and symptoms specifically, nasal congestion and congested nose with runny discharge.

Table 22. Total variance, loadings and eigenvalues of components

Components	Initial Eigenvalues			Extraction Sums of Loadings		
	Total	% of Variance	Cumulative %	Total	% of Variance	Cumulative %
1	5.357	48.700	48.700	5.357	48.700	48.700
2	1.235	11.225	59.926	1.235	11.225	59.926
3	1.029	9.353	69.279	1.029	9.353	69.279
4	.782	7.105	76.385			
5	.698	6.341	82.726			
6	.525	4.772	87.497			
7	.416	3.784	91.281			
8	.328	2.983	94.264			
9	.288	2.614	96.878			
10	.222	2.014	98.892			
11	.122	1.108	100.000			

The highest loadings with the characteristics of Component 1 are Xi Xin, Xin Yi, Bai Zhi, Bai Bu, Cang Er Zi, Chuan Xiong, Huang Qi, Fang Feng, Gua Di, Bo He and Bai Zhu (in descending order). All these herbs share characteristics of managing AR-like signs and symptoms associated with effective treatment to nasal congestion which are relative to Component 1. Negative loading is depicted for Bai Xian Pi in Component 1 which means that this herb may not necessarily be effective for the treatment of nasal congestion. Traditionally, in CM diagnostics, Bai Xian Pi is used to treat conditions related to oedema. Similarly, herbs associated with Component 2 are Chuan Xiong, Bai Xian Pi, Gua Di and Huang Qi (in descending order). Both Huang Qi and Gua Di have positive loadings of both Component 1 and 2 but with stronger influence in Component 1, this could be an indication of its versatility in its remedies. These herbs are associated with treatment for other AR signs rather than nasal

congestion. It is noted that although Chuan Xiong possesses both Component 1 and 2, it has a higher loadings of Component 2 (10.03312) than 1 (2.22028). This could be interpreted that it may be more effective in treating other AR-like signs and symptoms than nasal congestion. (Table 23).

Table 23. Component loadings matrix of herbs

Herbs	**Principal Component 1**	**Principal Component 2**
Xi Xin (*Asari Radix et Rhizoma*)	9.0156	-0.41758
Xin Yi (*Magnoliae Flos*)	3.51007	-1.17409
Bai Zhi (*Angelicae Dahuricae Radix*)	3.03387	-2.24648
Bai Bu (*Stemonae Radix*)	2.96231	-0.28186
Cang Er Zi (*Xanthii Fructus*)	2.23757	-0.86863
Chuan Xiong (*Ligustici Rhizoma*)	2.22028	10.03312
Huang Qi *(Astragali Radix*)	2.17804	0.37503
Fang Feng (*Saposhinikoviae Radix*)	2.09358	-1.7895
Gua Di (*Pedicellus Trichosanthis*)	1.99094	0.94858
Bo He (*Mentae Haplocalysis Herba*)	1.96368	-2.30418
Bai Zhu (*Atractylodis Macrocephalae Radix*)	1.42645	-0.16902
Bai Xian Pi (*Dictamni Cortex*)	-0.11798	2.77305

In Figure 58, a distinct cluster of herbs is detectable near 0. From this, it can be interpreted that this group of herbs all possess the same qualities of treating AR-like signs and symptoms, which indicates that these herbs treat sneeze, congested nose with runny nose discharge, rhinosinusitis, nasal congestion, itchy nose, allergic rhinitis, postnasal drips, headache, and eye pain, pain the nose and red nose with the same effect. Based on the PCA, amid all the herbs evaluated, all herbs exhibited similar levels of efficacy but there are few variations in the treatment of the AR-like signs and symptoms with the exception of the few herbs such as Xin Yi, Bai Bu, Cang Er Zi, Chuan Xiong, Huang Qi, Fang Feng, Gua Di, Bo He and Bai Zhu. Xin Yi, having the

second largest loadings PC1 axis, also depicted a high pattern of association with possible effective treatment of nasal congestion (Figure 58).

The PC1 on x-axis marks the circle of dimension at 48% while PC2 on y-axis is 11%. The PCA depicted the two herbs that demonstrated largest variations in PC1 and PC2, Xi Xin and Chuan Xiong; respectively. In fact, the huge inertia of Xi Xin on PC1 marks its dimension away from the rest of the herbs indicates a pattern that Xi Xin may feature a strong profile in treating AR-like signs and symptoms, while Chuan Xiong with higher coordinates on PC2 is inversely correlated to Xi Xin in the treatment of AR signs and symptoms (Figure 58).

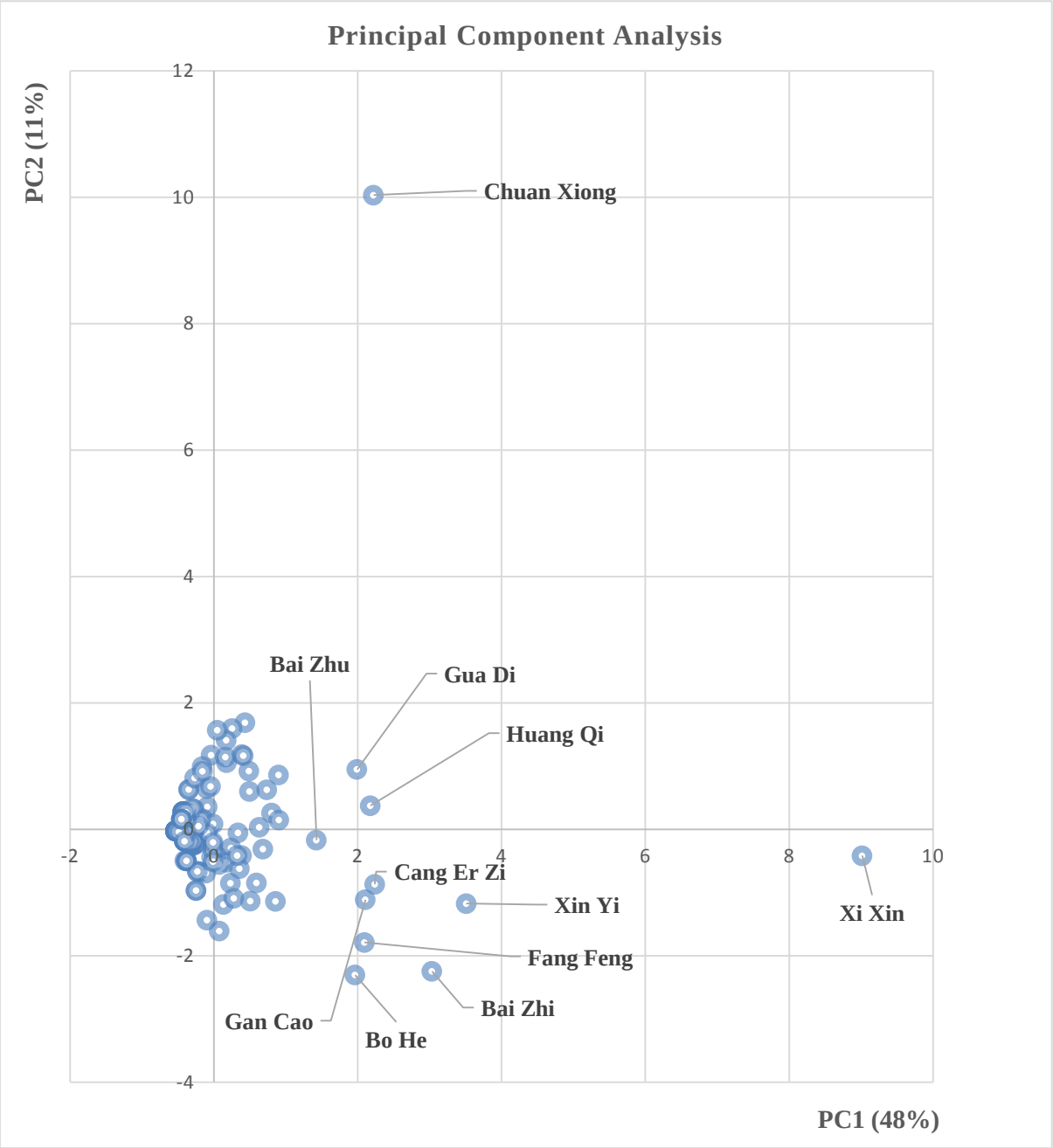


Figure 58. Principal component analysis of 163 herbs from ZHYD and ZGBCQS

7.5. Hierarchical cluster analysis of herbs

The dendrogram is a graphical representation of cluster pattern analysis produced by SPSS analytics, which employs the agglomeration schedule to identify a set pattern which components or cases (herbs) are grouped together. Scale distance is determined by using squared Euclidian distance and between-groups distances to highlight importance of large distances and cluster all data points, respectively. The compound clusters are formed by joining individual compounds or existing compound clusters with the join point known as node (Nonlinear Dynamics, 2016). Based on the hierarchical analytics, three clusters were identified with herbs Qing Mo to Chang Pu grouped cluster 1, Pi Ba to Xiong Huang in cluster 2 and cluster 3 included only Xin Yi and Xi Xin (Table 24). Cluster 1 demonstrates that all the herbs were similar in their effects. Cluster 1 and Cluster 3 indicated no significant clustering with the exception that Xin Yi was merged with cluster 1, which may be due to the fact that Xin Yi shared the same characteristics in treating AR-like conditions. Yet, cluster 3 was markedly dissimilar from the rest of the herbs. Overall, the pattern clusters demonstrated although all the herbs are likely to treat AR-like and symptoms, except Xin Yi and Xi Xin are different. Both Xi Xin and Xin Yi are regarded as outliers. Although is clustered as an outliers, Xin Yi is correlated with cluster 2 herbs such as Pi Ba, Sheng Jiang, Tong Cao, Bo He, Fang Feng, Gua Di, Bai Zhi, Gan Cao, Cang Er Zi, Chuan Xiong, Huang Qi, Fu Zi, Jie Gen, Nan Xing, Cong Bai, Mu Tong, Gan Jiang, Ren Shen, Qiang Huo and Xiong Huang. This could be interpreted that Xi Xin has similar effects on the components 1 and 2 with linkage to the aforementioned herbs and Xin Yi (Figure 59).

Table 24. Lists of clustered herbs extracted from dendrogram

Cluster 1	Cluster 2	Cluster 3
• Fu Di Qing Mo (*) • Zhu Ye (*Callicarpae Formosanae Folium*) • Ma You (Sesame oil)) • Shi Gao (*Gypsum Fibrosum*) • Mai Dong (*Ophiopogonis Radix*) • Cong Xian (Garlic juice) • Ma Niao (Horse urine) • Ze Zi Gen (*) • Bi Ma Ren (*Ricini Semen*) • Pi Pa Ye (*Eriobotryae Folium*) • Ya Cao (*Commelinae Herba*) • Da Suan (Garlic) • Gao Ben (*Ligustici Rhizoma et Radix*) • Zhi Gan Cao (*Glycyrrhizae Radix et Rhizoma*) • Zhi Shi (*Aurantii Fructus Immaturus*) • Chen Ju Pi (*Citri Reticulatae Pericarpium*) • Gan Song (*Nardostachyos Radix et Rhizoma*) • Yuan Zhi (*Polygalae Radix*) • Ou Jie Hui (*Nelumbinis Rhizomatis Nodus*-ash) • Ting Xiang (Clove) • Gan Hu Lu (*Trigonellae Foeni-graeci*) • Po Xiao (*) • Zao Jiao (*Gleditsiae*) • Da Huang (*Rhei Radix et Rhizoma*) • Ji Zi (Chicken) • Mu Xiang (*Aucklandiae Radix*) • Shi Xiao (*) • Liu Huang (Sulfur) • Chuan Wu (*Aconiti Radix*) • Gua Zi Ren (*Trichosanthis Semen*) • Huo Po (*Magnoliae Officinalis Cortex*) • Jiang Can (*Bombyx Batryticatus*) • Cang Tui (*Cicadae Periostracum*) • Huo Xiang Ye (*Agastaches Herba Folium*) • Da Zao (*Jujubae Fructus*) • Qian Hu (*Peucedani Radix*) • Lian Qiao (*Forsythiae Fructus*) • Yuan Shen (*) • Bai Shao (*Paeoniae Radix Alba*) • Shu Jiao (*) • Tian Dong (*Asparagi Radix*)	• Bi Ba (*Piperis Longi Fructus*) • Sheng Jiang (*Zingiberis Rhizoma Recens*) • Tong Cao (*Tetrapanacis Medulla*) • Bo He (*Menthae Haplocalycis Herba*) • Fang Feng (*Saposhnikoviae Radix*) • Gua Di (*Pedicellus Trichosanthis)* • Bai Zhi (*Angelicae Dahuricae Radix*) • Gan Cao (*Glycyrrhizae Radix et Rhizoma*) • Cang Er Zi (*Xanthii Fructus)* • Chuan Xiong (*Ligustici Rhizoma*) • Huang Qi (*Astragli Radix*) • Fu Zi (*Aconiti Lateralis Radix Praeparata*) • Jie Geng (*Platycodonis Radix*) • Nan Xing (*Arisaema Cum* Bile/*Arisaematis Rhizoma*) • Cong Bai (*Bulbus Allii*) • Mu Tong (*Akebiae Caulis*) • Gan Jiang (*Zingiberis Rhizoma*) • Ren Shen (*Ginseng Radix et Rhizoma*) • Qiang Huo (*Notopterygii Rhizoma et Radix*) • Xiong Huang (*Realgar*)	• Xi Xin (*Asari Radix et Rhizoma*) • Xin Xi (*Magnoliae Flos*)

Cluster 1	Cluster 2	Cluster 3
• Long Nao Xiang (*) • Qing Shou Cao Hua Sheng (Hand-fried peanuts) • Mu Gua (*Chaenomelis Fructus*) • Gou Tou Hui (Canine skull-ash) • Ai Ye (*Artemisiae Argyi Folium*) • Shi Lü (Jadeite) • Yang Fei (Goat's Lungs) • Zhu Ya (Pig's teeth) • Shui Jin (*) • Xuan Shen (*Scrophulariae Radix)* • Qiang Liang (*) • Qing Yu Dan (*) • Li Lu (*) • Man Jing Zi (*Viticis Fructus*) • Ku Qin (*) • Kuan Dong Hua (*Farfarae Flos*) • He Zi (*Chebulae Fructus*) • Ji Zi Jing (Chicken essence) • Dou Chi (*) • Fu Mo (*) • Bing Lang (*Arecae Semen*) • Bei Zi (*) • Tie Fen (Iron powder) • Bei Bu (*) • Ku Gua (*) • Chai Hu (*Bupleuri Radix*) • Gan Ju (*) • Sang Ji Hua Rui (*Taxilli*) • Tie Suo (Iron) • Chuan Jiao (*) • Quan Xie (Scorpion) • Ren Zhong Bai (Human urinary sediments) • Ma Zi Ren (*) • Qiu Yin (Earthworm) • Geng Mi (Cooked rice) • Yang Sui (*) • Zhen Zhu (*Margarita*) • Hai Er Cha (*Catechu*) • Hua Fen (*) • Di Yu (*Sanguisorbae Radix*) • Lu Er (*) • Qing Niu Jiao (*Bubali Cornu*) • Fu Ling (*Poria*) • Xun Cao (*) • Zao Jia (*) • Xiao Ji (*Cirsii Herba*) • Zhu Sha (Cinnabaris) • Bi Cheng Qie (*Litseae Fructus*) • Lu Xiang (*) • Fu Di Mo Shui (*) • Shan Zhu Yu (*Corni Fructus*)		

Cluster 1	Cluster 2	Cluster 3
• Dang Gui (*Angelicae Sinensis Radix*) • Fan Shi (*) • Shi Hu (*Dendrobii Caulis*) • Rou Gui (*Cinnamomi Cortex*) • Su Ye (*Perillae Folium*) • Gou Rou (Canine's meat) • Ku Fan (*) • Shao Mo Xue Hui (*) • Bi Ma Zi (*Ricini Semen*) • Huang Lian (*Coptidis Rhizoma*) • Qing Niu Xi (*) • Cang Zhu (*Atractylodis Rhizoma*) • Jiu Qin (Alcohol essence) • Xin Yi Ren (*) • Bei Mu (*Fritillariae Ussuriensis Bulbus/ Fritillariae Thunbergii Bulbus*) • Xiang Fu (*Cyperi Rhizoma*) • Di Huang (*Rehmanniae Radix*) • Ku Shen (*Sophorae Flavescentis Radix*) • Tao Ren (*Persicae Semen*) • Bai Fan (*) • Lu Xiang (*) • Cao Tou Wu (*Aconiti Kusnezoffii Radix*) • Huang Dan (*) • Ge Gen (*Puerariae Lobatae Radix*) • Jing Jie (*Schizonepetae Herba*) • Zhi Zi (*Gardeniae Fructus*) • Ma Huang (*Ephedrae Herba*) • Gui (*Cinnamomi Ramulus*) • Rui He (*) • Gui Xin (*) • Ban Xia (*Pinelliae Rhizoma*) • Ji Li (*Tribuli Fructus*) • Sheng Ma (*Cimicifugae Rhizoma*) • E Bu Shi Cao (*Centipedae Herba*) • Gan Shi (*) • Ju Hua (*Chrysanthemi Flos*) • Bai Zhu (*Atractylodis Macrocephalae Rhizoma*) • Chang Pu (*Acori Tatarinowii Rhizoma*)		

* Latin names were not available

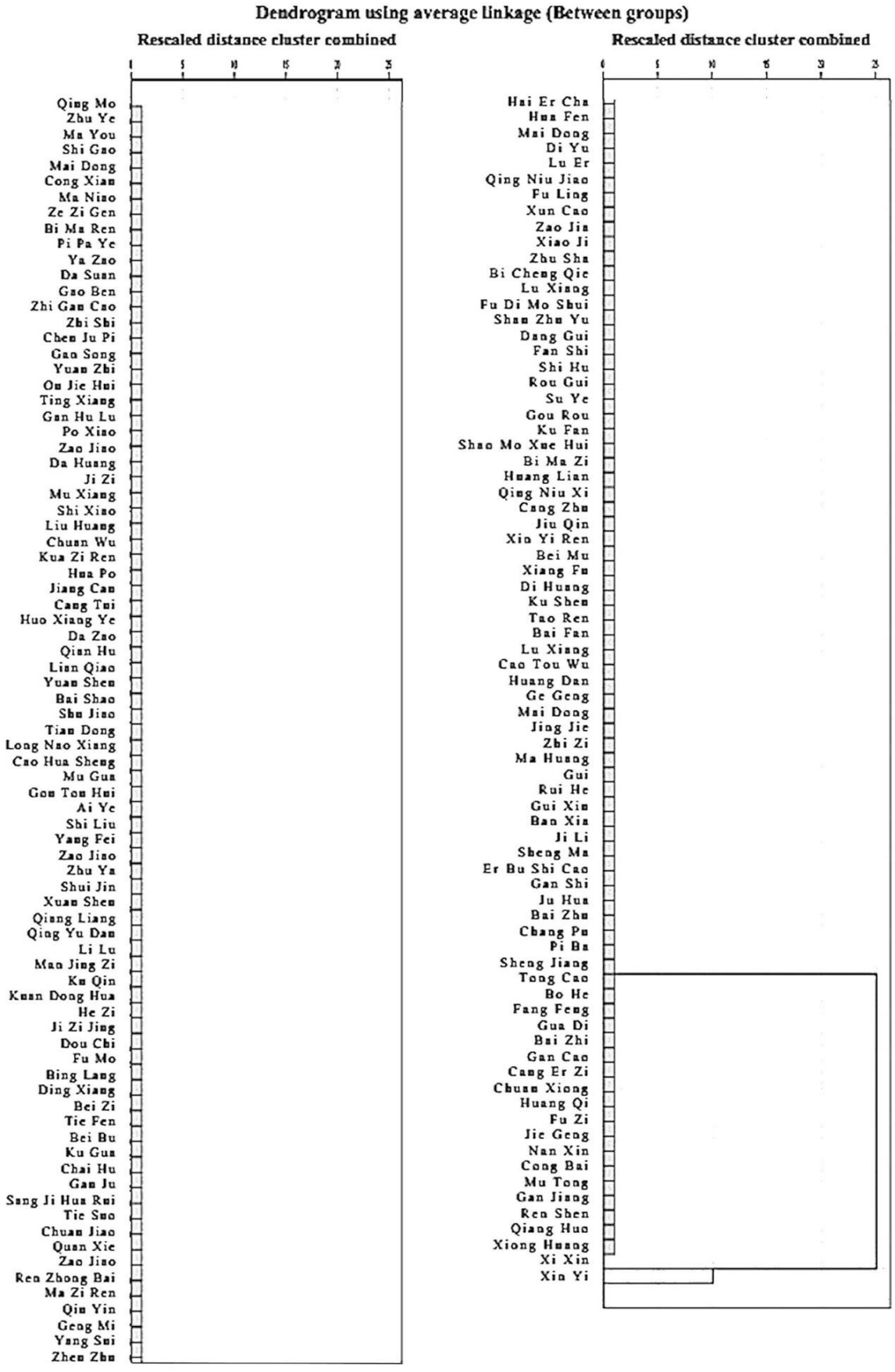


Figure 59. Dendrogram using average linkage (between groups) rescaled distance cluster combined

7.6. Discussion

Each of the volumes of ZGBCQS may consist of more than one book. It is not uncommon to expect that same books in different collections may have the same titles (May et al., 2013). However, the content may be presented differently. Both ZHYD and ZGBCQS, the former being digital format and the latter in paperback hardcopies, do not contain any index nor a structured list of titles of books for access. The ZHYD sorely lacks bibliographic data for the purpose of referencing and systematic search (May et al., 2013). The lack of bibliographic data in ZGBCQS and index of non-structured list of titles in ZHYD are in part due to nature of the articles or writings presented in these texts. Each citation of the articles is a representation of a clinical instance which was recorded by the author(s) or author-clinician(s). It is common to find disparate writings by author(s) and clinician-author(s) in small parts with excerpts of their knowledge and findings recorded in the classical texts years later after the original writer had passed on. Many of the texts were compiled together under same titles with contributions from different writers with little information of the dates, rendering structured indexing an arduous task for research purposes. Moreover, interpretation of these medical texts is also subjected to many challenges: vocabulary, semantics, and lexical context.

Chinese medical historical texts, ZHYD and ZGBCQS, both are of great significance and relevance in the clinical practice of CM. Connotative descriptions of syndromes in CM stem from these texts and are still used in current practice. Although these CM historical diagnoses may not fit the framework of modern medicine, its context is still meaningful in disease treatment. It provides a backdrop to the types of disease to which the treatments were used, and an insight to the types of natural products that were effective. Most importantly, it creates opportunities to identify conditions that could parallel modern biological diseases that still lack the right drug efficacy.

The reliability of retrospective diagnosis derived from these historical texts is dependent on several factors: eye-witness testimony; clear descriptions of signs and symptoms of the disease, and minimal evidence for modifying description to match medical views of period, presence of one or more virtually diagnostic symptoms, and record of any epidemiological observation given (Mitchell, 2011). From a CM clinical perspective, the retrospective diagnoses in the CM medical texts are able to fulfil the criteria for reliability. It is important to highlight that this project does not entail an exercise of textual analysis but to conduct a text mining extracting data on the citations of AR-like signs and symptoms.

A total of 163 herbs were identified for the management for AR-like signs and symptoms in the CM classical texts which were closely associated with AR in modern diagnosis. Component analysis indicated all the herbs consisted of homogenous characteristics in treating AR-like signs and symptoms. This could be interpreted that either all herbs were just as effective in treating AR-like symptoms or not at all. Herbs with eigenvalue of greater than 1 on x-axis is of a level of significance, namely; Xi Xin, Xin Yi, Bai Zhi, Fang Feng, Huang Qi, Fang Feng, Cang Er Zi, Bai Zhu, Bo He, Gan Cao and Gua Di. All of these herbs share prevailing characteristics of Component 1 which may address certain traits in addressing AR-like signs and symptoms. Only two herbs exhibited great variations; Xi Xin (Component 1) and Chuan Xiong (Component 2). The magnitude on the x-axis which highlights the vast distance from the rest of the herbs indicates Xi Xin is entirely dissimilar and could potentially consist of characteristics of more than addressing AR-like signs and symptoms. The Euclidean distance showed a near 10-fold inertia for Chuan Xiong and Xi Xin from the rest of the herbs. The effectiveness of Xi Xin has been described as miraculous (Shen Xiao; 神效) in the classical texts. It has the attributes of not just treating nasal congestion but the varied types of conditions associated with nasal congestion and severe nose blockage such as yellow-green discharge (a sign of inflammatory infection) and clear runny nasal discharge. Aside from treating AR-like

symptoms, descriptions matching dyspnoea and chest discomfort were also associated with Xi Xin. In contrast, Chuan Xiong leans closer to the y-axis with strong influence of Component 2. The variation of the component is lesser than Xi Xin, it is differentiated from the other herbs based on the proximity to the y-axis in the pattern analysis. The inclusion of Chuan Xiong in the classical texts and its variance of 12% is an indication of its limited role in treatment of AR compared to Xi Xin.

The HCA in the dendrogram appears to have its own set pattern of clustering herbs for its remedies. Almost all the herbs share a similar remedy for AR-like management. A total of 139 herbs are grouped in cluster 1 with join node of less than 1, indicating little difference amongst the herbs in its function for treatment. The graphical representation showed two outliers which are on its own; Xi Xin and Xin Yi. Both of these herbs are distinct in its management of treatment of AR signs and symptoms. Particularly, these two herbs have also been identified as most commonly used herbs used for AR management in the SR of modern clinical studies. It would be meaningful to analyse the characteristics of both Component 1 and Component 2 in these herbs further either in pharmacological, clinical or genotyping analyses to further determine their variations in their respective clusters.

Chapter 8 General discussion

This chapter discusses the results of the reviews of clinical studies, experimental and classical literature in this project as well as the applicability and quality of the evidence.

8.1. Summary of main results

The SR provided a deep insight as to the effects of CHM for the treatment of AR in RCTs. A total of 62 RCTs were included in the SR according to selection criteria and all except one (Jiang 1997) were included in the meta-analyses as it did not apply any continuous or dichotomous data for quantifying its results. The comparisons consisted of CHM versus placebo, WM or other therapies, with or without co-interventions. The outcome measures composed of five domains: improvement of symptoms, quality of life, rescue medication use, IgE levels and adverse events. Durations of immediate, short-term, intermediate and long-term were also used as yardstick for the measure of the domains when possible. The outcome of this review presented mixed results for the clinical effects of CHM.

The scientific community has long regarded the randomised, double-blind, placebo-controlled clinical trial as the "gold standard" of scientific methodology for testing therapeutic effects of interventions (West et al., 2010). Eight included studies adopted such ideal design. However, due to the diverse outcome measures selected across those studies, data synthesis was unlikely performed.

Promising results surfaced in the comparison of CHM versus Western medicine. Meta-analyses reflected significant clinical effects of CHM for global symptom improvement at immediate (15 trials), short-term (14 trials), intermediate (four trials) but not long-term (four trials) follow-ups. Particularly, subgroup analyses demonstrated CHM was more beneficial for global

symptom improvement when compared to orally taken anti-histamines (including Cetirizine, Hismanal, Ketotifen, Loratadine, Desloratadine and Triprolidine) for immediate (11 trials) and short-term (nine trials) follow-up. It is noted that Hismanal (Astemizole) was discontinued in the US in 1999 due to cardiovascular risks and its adverse effects according to the Food and Drug Administration (U.S. Food and Drug Administration, 1999). When CHM was combined with other therapy in comparison to same other therapy alone, CHM demonstrated more additional effects in improving global symptom across all duration of follow-ups.

Although CM provides individualised treatment to patients with a focus on the differentiation of syndrome, this protocol was only incorporated in less than 7% of included studies (four out of 62 RCTs). Due to the limited studies, it is not surprising that synthesised data could not illustrate CHM combined group's effects for subgroup studies involving syndrome differentiation when compared to those studies without syndrome differentiation.

In terms of quality of life, CHM was highly favourable for PAR in physical functioning, physical role and general health. IgE levels tended to favour WM, however, there was no direct correlation between the total serum IgE concentration and the symptom improvement. Further meta-analysis could not be conducted on use of rescue medication (95% of studies), quality of life (94% of studies) and IgE domains (98% of studies) as a lack of data existed in the RCTs. No severe adverse events were noticed across all the included studies.

The overall findings of the SR of RCTs demonstrated that CHM might be effective and safe for AR management when used orally on its own or as an adjunct therapy to WM. However, it is important to note that the positive results could essentially be interfered by high/unclear risk of bias in the studies. The promising results should be interpreted with great caution.

The text mining exercise of classical texts provided an invaluable insight into retrospective diagnosis and the remedies for AR. A total of 1,687 articles were identified with descriptions related to AR-like signs and symptoms. Both the PCA and HCA demonstrated a few herbs might share similar components which facilitated the efficacy of AR. Component 1 herbs were Xi Xin, Xin Yi, Bai Zhi, Bai Bu, Cang Er Zi, Chuan Xiong, Fang Feng, Huang Qi, Gua Di, Bo He and Bai Zhu (in descending order) with Component 2 influence in Chuan Xiong, Bai Xian Pi, Gua Di and Huang Qi (in descending order). The dendrogram also definitively cast Xi Xin as one of the outliers along with Xin Yi. While the clustering analysis demonstrates all the other herbs were able to provide the similar effects. Xi Xin was distinctive on its own. However, Xi Xin is famed for its dose-related adverse effects. Experimental results have demonstrated that AA-I in Xi Xin was within 3.1 mg to 26.6 mg, indicating negligible levels of toxicity. AA-I toxicity was concentrated, in the aerial parts rather than the roots, and in methanol extracts than water extracts. Water extraction which is synonymous to decoction preparation could further reduce the toxicity. Statistical significance indicated Xi Xin could possibly be able to provide more than just mere remedy of AR symptoms. Based on these results, this could be the platform for future studies to explore the compounds and the pharmacological targets, and dose-related safety of Xi Xin in order to ascertain its effects. A rationale based risk-benefit assessment on and regulated prescription of Xi Xin under scheduled drugs would be a better justification than the current blanket ban of this herb.

It is undoubtable that evidence in both modern literature and classical texts suggest CHM could be a good form of remedy for the treatment of AR. In spite of the heterogeneity, varied experimental studies demonstrated the naturally occurring compounds have more to offer than just mere management of AR.

8.2. Overall completeness and applicability of evidence

This rigorous SR is extensive and comprehensive in its search and meta-analyses. Searches included 17 English and three Chinese databases to identify all the up-to-date RCTs. Varied forms of Chinese herbs with oral and/or external administration for the treatment of patients with SAR and/or PAR of any age were also considered. Nearly 75% of the studies (47 out of 62) did not categorise their participants into SAR or PAR and as a result, these studies were excluded from subgroup analysis according to the classification of AR. Except for seven studies did not provide age details of participants, more than 50% of the remaining RCTs mixed the children and adults as their subjects. This rendered subgroup analysis as per age group unfeasible.

The CHMs that were popular in the RCTs differ from those of the classical texts. A comparison of the top ten herbs used for the management of AR in the SR and classical literature are summarised below (Table 24). It is noted that seven common herbs have been identified during the process of this project. They are: Huang Qi, Fang Feng, Xin Yi, Bai Zhi, Cang Er Zi, Gan Cao and Xi Xin.

Table 25. Comparisons of top ten herbs used for the management of AR in the SR and classical literature

Rank	Top ten herbs from SR	Top ten herbs from classical literature
1.	Huang Qi (*Astragali Radix*)	Xi Xin(*Asari Radix et Rhizoma*)
2.	Fang Feng (*Saposhnikoviae Radix*)	Xin Yi (*Magnoliae Flos*)
3.	Xin Yi (*Magnoliae Flos*) Bai Zhi (*Angelicae Dahuricae Radix*)	Bai Zhi (*Angelicae Dahuricae Radix*)
4.	Cang Er Zi (*Xanthii Fructus*)	Bo He (*Menthae Haplocalycis Herba*) Gua Di (*Pedicellus Trichosanthis*)
5.	Gan Cao (*Glycyrrhizae Radix et Rhizoma*)	Gan Cao (*Glycyrrhizae Radix et Rhizoma*)
6.	Xi Xin (*Asari Radix et Rhizoma*)	Chuan Xiong (*Ligustici Rhizoma*) Fang Feng (*Saposhnikoviae Radix*)
7.	Dang Shen (*Codonopsis Radix*)	Huang Qi (*Astragali Radix*)
8.	Wu Wei Zi (*Schisandrae Chinensis Fructus*)	Cang Er Zi (*Xanthi Fructus*) Sheng Jiang (*Zingiberis Rhizoma Recens*)
9.	He Zi (*Chebulae Fructus*)	Fu Zi (*Aconiti Lateralis Radix Preparata*) Tong Cao (*Tetrapanacis Medulla*)
10.	Chan Tui/yi (*Cicadae Periostracum*)	Jie Geng (*Platycodonis Radix*) Ren Shen (*Ginseng Radix*)

It is worth noting that the seven herbs used in the modern times were similar in ancient times by the CM physicians. In CM diagnostics, the combination of Huang Qi, Fang Feng, Xin Yi, Bai Zhi and Cang Er Zi is indicated to protect tonify Qi, dispel dampness, protect the Wei Qi and secure the exterior. Xi Xin warms the Lung and transforms phlegm. Gan Cao is commonly used to harmonise the formulation; but as a herb it can tonify the Spleen, reinforce Qi and stop cough. The substitution of Ren Shen in RCTs in the place of Dang Shen (as both herbs tonify Qi) is clear, as Ren Shen is extremely costly in current times. It could be seen from Table 24 that CM physicians of the past prescribed warm herbs Sheng Jiang and Fu Zi to AR patients as cold predominates the CM pathogenesis of AR. Fu Zi is deemed in CM to possess excellent properties of warming the interior and expelling cold; however, this herb is banned in many

countries due to its toxicity. Gua Di, Tong Cao and Jie Geng can relieve nasal congestion. Current use of Wu Wei Zi and He Zi targets astringing where it is deemed these herbs constrain the Lung Qi and stop coughing. Chan Tui relieved wind-heat (a condition which wind-cold transformed into) and itchiness in AR. In contrast, Bo He was used to relieve wind-heat in ancient times.

The data mining of the classical literature reflected Xi Xin as the top choice herb used by CM physicians in ancient times whereas Huang Qi has replaced Xi Xin in modern days. The use of Xi Xin in modern RCTs has relegated in part due to the strict regulatory restriction owing to the outcome of the scientific research of its toxic properties. In mainland China, the dosage is restricted within 1 to 3 g. This herb is currently scheduled in Australia and Europe. The popular use of Huang Qi could largely be attributed to its capabilities to tonify Qi, to rectify a major complaint of fatigue syndrome that often accompanies AR symptoms.

The RCTs conducted in mainland China tended to focus on the effective rate to present CHM's effects whilst the RCTs performed outside mainland China assessed CHM's effects with different outcome measures (such as symptom score, quality of life and rescue medication score) by completing questionnaires. The effective rate is a composite outcome measure which has some limitations. For instance, the total effective rate was used to represent the global symptom improvement which makes changes of individual symptoms invisible and it is difficult to determine which component CHMs took effects on. Separate reporting of each individual symptom will make comparison of different studies feasible and further provide more detailed evidence to clinical practice. The use of the effective rate as an outcome assessment indicator may be due to lack of validated instrument for the measurement. Therefore, guidelines with appropriate outcome assessment tools need to be developed and promoted to facilitate clinical practice and research.

Due to the large variety of confounding variables, such as age (two to 82), sample size (20 to 564), treatment period (from two weeks to three months), different formulations and low quality of evidence for the outcomes (more discussion in 8.3), no ideal standard treatment regime for AR management can be determined.

8.3. Quality of evidence

All the included studies are embedded with methodological limitations and the quality of evidence was consistently low across the board.

Methodological issues are reflected by high or unclear risk of bias in selection (random sequence and/or allocation concealment), performance (except RCTs comparing CHM with placebo), detection, attrition and reporting across all the studies. It is noteworthy that the RCTs comparing CHM with placebo demonstrated relatively better quality. All these studies adopted double-blind design which led to low risk of performance bias. Three of them had low risk of selection bias for allocation concealment (Baba 1995; Hu 2002; Matkovic 2010). Particularly, the Baba 1995 study was a multi-centre (62 centres) and large scale (n = 220) RCT. However, the quality of trials comparing CHM with conventional therapies (drugs or immunotherapy), or CHM plus other therapy with same other therapy only, with or without co-interventions, was generally low or very low.

Confounding variables in quality of reporting, participant attributes (i.e. age, gender, diagnosis, co-morbidity) and treatment protocol (i.e. co-intervention, formulation, treatment protocol) may contribute to the substantial clinical heterogeneity in this review. Clinical heterogeneity, also described as clinical diversity is mainly due to the variability in the participants, interventions and outcomes (Higgins & Green, 2011). Patient level data in the studies are sorely lacking in these RCTs. The Agency of Healthcare Research and Quality recommends analysis

of individual patient-level data in meta-analysis for better assessment of clinical heterogeneity (West et al., 2010). Despite the presence of statistical heterogeneity arising from clinical heterogeneity, CHMs for AR seem effective as an adjunct therapeutic option. It is transparent that based on the evidence of the SR, more rigorously designed RCTs are needed.

8.4. Comparative scrutiny with other studies/reviews

Insofar, only two reviews have been conducted in relations to CHM for the management of AR (Guo, Pittler, & Ernst, 2007; S. Wang, Tang, Qian, & Fan, 2012). Guo and his colleagues (2007) conducted a search on six English databases but did not affix a commencement date for the literature except for the end date (no date mentioned to Nov 2005) whilst Wang and her colleagues S. Wang et al. (2012) accessed three English databases (from 1999 to Jan 2011) and two Chinese databases (1999 to Feb 2011). The current review performed a more comprehensive literature search for 17 English databases and three Chinese databases (from respective inceptions to April 2016). The Guo 2007 review evaluated a spectrum of phytomedicinal herbs from traditional to Western herbs; RCTs included were placebo controlled or controlled against another active treatment. There was no information on the subgroup analysis conducted specifically for CHM. Wang and her colleagues (2012) narrowed the assessment of RCTs to comparison of CHM to placebo for PAR only. The extent of the scope of analysis has limited a spectrum of the AR conditions such as SAR.

The Guo 2007 review included 16 double-blind RCTs, covering both Western and Chinese herbs. Three trials using Chinese herbs in Guo's review were also included in the current review (Baba 1995; Hu 2002; Xue 2003a). The Guo's review applied Jadad's five-point scale to evaluate the methodological quality of includes studies and those three RCTs were given a score; four, five and five, respectively. The current review adopted the Cochrane Handbook's instructions and assessed the risk of bias of each study. More than 90% of the studies consist of

unclear risk of bias in selection (allocation concealment) and performance as well as in categories of selection (random sequence generation), detection, attrition and reporting. Baba 1995 had low risk of bias in selection (allocation concealment) and performance, and unclear risk of bias in selection (random sequence generation), detection, attrition and reporting. The Hu 2002 trial had low risk of bias in selection (both random sequence generation and allocation concealment), performance and detection, unclear risk of reporting bias and high risk of attrition bias. The Xue 2003a study had low risk of selection bias (random sequence generation) and performance bias, unclear risk of selection bias (allocation concealment), detection and reporting bias, and high risk of attrition bias.

The Wang 2012 review also applied Jadad's quality assessment for seven PAR trials in the meta-analysis. It reported a positive outcome for CHM in decreasing nasal symptom for all studies (Chui 2010; Hu 2002; Yang 2008; Yang 2010; Zhang 2004; Zhao 2009) when compared to placebo, except for Jung 2011 (Wang et al, 2012). It is important to note that four trials (Zhang 2004; Yang 2008; Yang 2010; Chui 2010) were not included studies in this current SR. Different selection criteria were the main reason for the exclusion of these trials. These trials did not qualify the criteria set out in this review. The inclusion of Zhang 2004 in Wang 2012 review raised question about their selection criteria as the comparison in the study involved active intervention (CHM formula) in the treatment group versus (another CHM formula-Ping Wei San) in the control group. Similarly, in Chui 2009, the comparison was active intervention (CHM external) vs (CHM herbs – Di Huang and Dang Shen). Although the writers mentioned that in Chui 2010, the two herbs in the control group (Di Huang and Dang Shen) were of no specific value to treatment. Particularly, evidence in this project have indicated that Dang Shen was identified as one of the top ten herbs used in ancient times to manage AR-like signs and symptoms. Moreover, it is worth noting that all herbs possess bioactive value, least to say, Di Huang and Dang Shen. Unclear inclusion criteria could render an invalid and inaccurate

analysis. Further, the Wang 2012 SR was limited, as the focus was on PAR studies. SAR trials were not included in the review, which is an important spectrum of AR. The non-inclusion of SAR limits the scope of the meta-analyses within the entire review of CHM used for the management of AR.

Similar to the previous reviews, this current SR also found some promising results of CHMs for treating AR. However, due to the high/unclear risks of bias and substantial heterogeneity across the included studies, large scale RCTs with rigorous design are required to confirm the findings.

Chapter 9 General conclusions

This chapter provides an overview of main achievements, strengths and limitations for the entire project on CHM for the management of AR and its implications for clinical practice and future research.

9.1. Main achievements

This project investigated the clinical effects and safety of CHM for AR management by conducting three reviews on SR on modern clinical and experimental studies as well as classical literature. The SR is an all-encompassing in its review approach employing rigours in Cochrane reviews of interventions. All systematic evaluations in the different types of AR, types of interventions, different duration follow-ups and risks of bias of the 62 RCTs are covered in the criteria. This is also the only SR that covers the entire of the spectrum of AR modern literature search (up to April 2016). The findings of the SR have identified some positive results of CHM for AR management as well as methodological weaknesses in the included studies.

The experimental studies reviewed all recently published *in vivo* and *in vitro* studies. The inclusion of WHO-selected medicinal herbs (only two of the herbs, Huang Qi and Xin Yi) provided a complete picture of the mechanisms of the five herbs identified from the SR.

The exhaustive search on the ZHYD and ZGBCQS which covered 1,687 articles with 294 articles yielded results of 163 herbs used for the management of AR in retrospective diagnoses. Analyses encompass not just mere frequency of citations but further analytics were undertaken to evaluate their potential for the management of AR.

9.2. Strengths and limitations

9.2.1. Strengths of the study

This project is a convergence of three reviews: a SR, a review of experimental studies and a review of the classical literature. The seamless progression of analyses of these three reviews provided a three-dimensional perspective, which no other projects have been undertaken. The SR provides a perspective on the outcomes of CHMs used in the RCTs and CHM's effects and safety while the review of the classical texts casts an insight into the types of herbs and usage in the treatment of AR-like signs and symptoms by means of modern analytics. Last, a review of the experimental studies provides a pharmacological perspective onto their multiple efficacies aside from treatment of AR. Much research has been carried out to screen herbs for its chemical compounds however, not all the research fulfils the strict rigours of specimen protocol. This review sets out strict criteria in the paper selections adhering to scientific standards for evaluation. This approach is to ensure scientific rigours on the process of screening the herbs are accurate without issues of contaminants.

9.2.2. Limitations of the study

Attempts to avoid bias during the review process by the reviewers (JK and AY) were strictly respected. However, potential bias may still exist owing to limited access to the databases other than English and Chinese languages. One Japanese study was translated by a staffer (AT). Overall, literature was limited to English and Chinese language databases due to language barrier in this project. It is possible that researchers in other Asian countries (such as Korea and Japan) might have conducted a number of clinical studies in CM. In view of the lack of resources on the part of the reviewers, existing studies in AR may not be identified in this current review.

Many subgroup analyses have been carried out in terms of types of AR, types of comparisons, myriad drug interventions, different assessment points and use of syndrome differentiation. One glaring difficulty was to conduct a subgroup analysis according to age groups as majority of studies involved participants with mixed age ranging from two to 80 plus years without providing stratified data.

The review for the experimental studies only evaluated the mechanisms of actions based on five top commonly used herbs for the treatment of AR from the RCTs. These five herbs are significant in the CHM for their effects and overall results unveil its versatility in targeting other system biology of diseases. Based on the results from the classical and modern literature, there are more herbs used in AR management, however, owing to the scope of this project, the review is confined to five herbs only.

9.3. Implication for clinical practice

Owing to the large variables, high heterogeneity and high/unclear risk of bias across the 62 included studies in SR, it is impossible to develop a standard treatment protocol of CHM for AR management to assist clinical practice.

The outcome of this project demonstrated CHMs, as an adjunct therapy could relieve AR signs and symptoms. CHMs oral and external when combined with WM oral and external were highly effective. However, there is no definitive conclusion to single out the most effective herb nor a standard formula, as varied herbal formulae administered in myriad forms were employed in the included RCTs. But results from herbs derived from the classical texts using analytics indicated Xi Xin could have the potential to offer relief for AR. Yupingfengsan (a wind-averting formula) was most commonly used in this review, with its three ingredients: Huang Qi (*Astragali Radix*), Fang Feng (*Saposhnikoviae Radix*) and Bai Zhu (*Atractylodis*

Macrocephalae Rhizoma). This herbal formula can be modified to fit the syndrome differentiation for the different types of AR in clinical practice. Practitioners need to be aware that AR's diagnosis, definition and physiological construct differ vastly from that of the models in Western medicine. Slow onset and prolonged effects of the bioactivities of herbal medicine proven in the experimental studies should be taken into consideration in assessment of CHMs for AR. When using toxic herbs such as Cang Er Zi and Xi Xin by products, toxicities leading to renal failures and carcinomas are real and evidence based. Considerations for use of Xi Xin could be rescheduled by the policymakers in the wake of the evidence presented in this review. For practitioners, deliberate caution should be exercised when dispensing Cang Er Zi or formulating with Cang Er Zi. High dosage and prolonged use should be avoided.

9.4. Implication for future research

This SR had discovered many weaknesses of RCTs in relation to sequence allocation generation, allocation concealment, blinding process of participants, personnel and outcome assessors, completeness of the outcome data, possibility of selective outcome reporting and other sources of reporting bias in the process of conducting a RCT. It is endeavoured that future RCTs are strongly advised to address these weaknesses before launching a RCT. Design protocols are highly recommended for all AR RCTs to avoid discrepancies between the design and the conduct.

The SR for AR also highlights one aspect of CM, which is the importance of syndrome differentiation for herbal formulation in RCTs. Syndrome differentiation is one of the key features in CM diagnosis and treatment. However, this has not been implemented in the design of RCTs. Although the subgroup analysis did not show distinctive difference in clinical effects when employing syndrome differentiation, this may be due to small number of included trials with syndrome differentiation as compared to those without it. Owing to the varied forms of

herbal administrations and the lack of syndrome differentiation, it is possible that the success of the treatment group is diminished. It is recommended that more trials with syndrome differentiation are required to render an accurate analysis of the effects of CHM.

In addition, there are seven common CHMs identified in the reviews of the RCTs and classical literature for effective management of AR. It is endeavoured that further clinical studies could be carried out on the testing the mechanisms of other herbs listed in the top ten herbs derived from the data mining of the classical texts. This would provide more evidence on the effects and validate their use in drug development.

References

Abbas, A. K., Lichtman, A. H., & Pillai, S. (2012). *Cellular and molecular immunology* (7th ed.). United States of America: Elsevier.

Abdi, H., & Williams, L. J. (2010). Principal component analysis. *Wiley Interdisciplinary Reviews: Computational Statistics, 2*(4), 433-459.

Adamic, K., Zidarn, M., Bajrovic, N., Erzen, R., Kopac, P., & Music, E. (2009). The local and systemic side-effects of venom and inhaled-allergen subcutaneous immunotherapy. *The Middle European Journal of Medicine [Wiener Klinische Wochenschrift], 121*(9-10), 357-360.

Ait-Khaled, N., Pearce, N., Anderson, H. R., Ellwood, P., Montefort, S., & Shah, J. (2009). Global map of the prevalence of symptoms of rhinoconjunctivitis in children: The International Study of Asthma and Allergies in Childhood (ISAAC) Phase Three. *Allergy, 64*, 123-148.

Alsowaidi, S., Abdulle, A., Shehab, A., Zuberbier, T., & Bernsen, R. (2010). Allergic rhinitis: prevalence and possible risk factors in a Gulf Arab population. *Allergy, 65*(2), 208-212. doi:10.1111/j.1398-9995.2009.02123.x

Andiappan, A. K., Nilsson, D., Halldén, C., De Yun, W., Säll, T., Cardell, L. O., & Tim, C. F. (2013). Investigating highly replicated asthma genes as candidate genes for allergic rhinitis. *BMC Medical Genetics, 14*(51), 1-9.

Andiappan, A. K., Wang, D. Y., Anantharaman, R., Parate, P., N.,, Suri, B. K., Low, H. Q., . . . Chew, F. T. (2011). Genome-wide association study for atopy and allergic rhinitis in a Singapore Chinese population. *PLoS One, 6*(5), e19719.

Asthma Australia. (2014). Rhinitis (hayfever). Retrieved from http://www.asthmaaustralia.org.au/rhinitis.aspx. Accessed 03 May 2015

Australia Health Bureau Statistics. (2012). Year Book Australia 2010. Australian Bureau of Statistics. (ABS Cat no 1301.0). Retrieved 2016, from Australian Bureau of Statistics http://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/1301.0~2012~Main%20Features~Health~22. Accessed 04 May 2015.

Australian Government Bureau of Meterology. (2016). Tracking Australia's climate and El Niño 2015. Retrieved from http://www.bom.gov.au/climate/updates/articles/a013.shtml. Accessed Oct 2016

Australian Institute of Health and Welfare. (2011). *Allergic rhinitis ('hayfever') in Australia*. (Cat no. ACM 23). Canberra: Australia Institute of Health and Welfare.

Baena-Cagnani, C., Finn, A., Potter, P., Menendez, R., Olsen, G., & Ruuth, E. (2003). Pollen aeroallergen sensitization in children with seasonal allergic rhinitis. *Journal of Allergy and Clinical Immunology, 111*(2, Supplement 1), S238-S239.

Baba, S., & Takasaka, T. (1995). Double-blind clinical trial of Sho-seiryu-to (TJ-19) for perennial nasal allergy. *Clinical Otolaryngology, 88*(3), 389-405.

Baldacci, S., Maio, S., Cerrai, S., Sarno, G., Baïz, N., Simoni, M., . . . Viegi, G. (2015). Allergy and asthma: Effects of the exposure to particulate matter and biological allergens. *Respiratory Medicine, 109*(9), 1089-1104.

Bao, A. C., Zhu, J. J., & Gong, Q. (2013). Clinical observation of Xiaoqinglong mixture in the treatment of allergic rhinitis [Xiaoqinglongtang heji zhiliao bianyingxing biyan de linchuang guancha]. *China Modern Medicine, 20*(31), 109-110.

Bara, I., Ozier, A., Tunon de Lara, J. M., Marthan, R., & Berger, P. (2010). Pathophysiology of bronchial smooth muscle remodelling in asthma. *European Respiratory Journal, 36*(5), 1174.

Barnes, P. J. (2010). Mechanisms and resistance in glucocorticoid control of inflammation. *Journal of Steroid Biochemistry and Molecular Biology, 120*(2–3), 76-85.

Baschant, U., & Tuckermann, J. (2010). The role of the glucocorticoid receptor in inflammation and immunity. *Journal of Steroid Biochemistry and Molecular Biology, 120*(2–3), 69-75.

Bedolla-Barajas, M., Morales-Romero, J., Pulido-Guillén, N. A., Robles-Figueroa, M., & Plascencia-Domínguez, B. R. (2016). Rhinitis as an associated factor for anxiety and depression amongst adults. *Brazilian Journal of Otorhinolaryngology*, 7.

Benninger, M. S., & Benninger, R. M. (2009). The impact of allergic rhinitis on sexual activity, sleep, and fatigue. *Allergy and Asthma Proceedings, 30*(4), 358-365.

Bhalla, P. L., & Singh, M. B. (2008). Biotechnology-based allergy diagnosis and vaccination. *Trends in Biotechnology, 26*(3), 153-161.

Black, J. A., Frézel, N., Dib-Hajj, S. D., & Waxman, S. G. (2012). Expression of Nav1.7 in DRG neurons extends from peripheral terminals in the skin to central preterminal branches and terminals in the dorsal horn. *Molecular Pain, 8*, 82-82.

Blaiss, M. S. (2000). Cognitive, social, and economic costs of allergic rhinitis. *Allergy and Asthma Proceedings, 21*(1), 7-13.

Blaiss, M. S. (2010). Allergic rhinitis: Direct and indirect costs. *Allergy and Asthma Proceedings, 31*(5), 375-380.

Bloomfield, S. F., Rook, G. A. W., Scott, E. A., Shanahan, F., Stanwell-Smith, R., & Turner, P. (2016). Time to abandon the hygiene hypothesis: new perspectives on allergic disease, the human microbiome, infectious disease prevention and the role of targeted hygiene. *Perspectives in Public Health, 136*(4), 213-224 212p.

Bousquet, J., Khaltaev, N., Cruz, A. A., Denburg, J., Fokkens, W., Togias, A., . . . H., Z. (2008). ARIA (Allergic rhinitis and its impact on asthma) 2008 update. Retrieved 27 Oct 2014, from World Health Organization, Global Allergy and Asthma European Network, AllerGen http://www.whiar.org/Documents&Resources.php. Accessed 27 Oct 2014.

Bousquet, J., van Cauwenberge, P., & Khaltaev, N. (2001). Allergic rhinitis and its impact on asthma. *Journal of Allergy and Clinical Immunology, 108*(5, Supplement), S147-S334.

Bousquet, J., Van Weel C, B., Cagnani, C., Demoly, P., Denburg, J., Fokkens, W. J., . . . Zhong, N. (2007). *Management of allergic rhinitis and its impact on asthma pocket guide in global primary care education* D. Nonikov (Ed.) Retrieved from www.whiar.org. Accessed 27 Oct 2014.

Brinkhaus, B., Ortiz, M., Witt, C. M., Roll, S., Linde, K., Pfab, F., . . . Willich, S. N. (2013). The effects of acupuncture on seasonal allergic rhinitis. *Annals of Internal Medicine, 158*(4), I-40.

Brozek, J. L., Bousquet, J., Baena-Cagnani, C. E., Bonini, S., Canonica, G. W., Casale, T. B., . . . Schünemann, H. J. (2010). Allergic rhinitis and its impact on asthma (ARIA) guidelines: 2010 revision. *The Journal of Allergy and cCinical Immunology, 126*(3), 466-476.

Bruhns, P., Frémont, S., & Daëron, M. (2005). Regulation of allergy by Fc receptors. *Current Opinion in Immunology, 17*(6), 662-669.

Burgess, J. A., Walters, E. H., Byrnes, G. B., Matheson, M. C., Jenkins, M. A., Wharton, C. L., . . . Dharmage, S. C. (2007). Childhood allergic rhinitis predicts asthma incidence and persistence to middle age: A longitudinal study. *The Journal of Allergy and Clinical Immunology, 120*(4), 863-869.

Cameron, L., Hamid, Q., Wright, E., Nakamura, Y., Christodoulopoulos, P., Muro, S., . . . Gould, H. (2000). Local synthesis of ϵ germline gene transcripts, IL-4, and IL-13 in allergic nasal mucosa after ex vivo allergen exposure. *Journal of Allergy and Clinical Immunology, 106*(1, Part 1), 46-52.

Cameron, L. A., Durham, S. R., Jacobson, M. R., Masuyama, K., Juliusson, S., Gould, H. J., . . . Hamid, Q. A. (1998). Expression of IL-4, Cϵ RNA, and Iϵ RNA in the nasal mucosa of patients with seasonal rhinitis: Effect of topical corticosteroids. *Journal of Allergy and Clinical Immunology, 101*(3), 330-336.

Canonica, G. W., Bousquet, J., Mullol, J., Scadding, G. K., & Virchow, J. C. (2007). A survey of the burden of allergic rhinitis in Europe. *Allergy, 62*, 17-25.

Cassell, H. R., & Katial, R. K. (2009). Intranasal antihistamines for allergic rhinitis: Examining the clinical impact. *Allergy and Asthma Proceedings, 30*(4), 349-357.

Cao, J. G., Ding, Y., & Cheng C.K. (2007). Clinical observation of Cang'erzi keli for the treatment of 30 cases with allergic rhinitis [Cang'erzi keli zhiliao bianyingxing biyan 30 li linchuang guancha]. *Xinan Junyi [Journal of Military Surgeon in Southwest China], 9*(3), 71-72.

Cao, Z. H., & Huang, F. Q. (2014). Xiangju joint capsule combined with claritin syrup treatment for 30 children with allergic rhinitis [Xiangju jiaonang lianhe kairuitan tangjiang zhiliao xiao'er guominxing biyan 30 li]. *Inner Mongolia Journal of Chinese Medicine [Neimonggu Zhongyiyao], 2*, 19-20.

Cassell, H. R., & Katial, R. K. (2009). Intranasal antihistamines for allergic rhinitis: Examining the clinical impact. *Allergy and Asthma Proceedings, 30*(4), 349-357.

Chen, C., Spriano, D., Lehmann, T., & Meier, B. (2009). Reduction of safrole and methyleugenol in Asari radix et rhizoma by decoction. *Forsch Komplementmed, 16*(3), 162-166.

Chen, J. J. (2012). *Effect of Chinese traditional medicine xingbi wenmin ningjiaoji in children with allergic rhinitis [Zhongyi xingbi wenmin ningjiaoji zhiliao xiao'er guominxing biyan de liaoxiao guancha]*. (Masters), Fujian University of Traditional Chinese Medicine, Fujian, China.

Chen, K., Luo H. X., Li, D. X., & Ye, B. X. (2004). The therapeutic effects of a combined therapy with radiofrequency thermocoagulation to the ethmoidal nerve under endoscope and Yupingfeng granule orally taking on perennial allergic rhinitis [Bineijingxia shepin rening shaiqian shenjing jiehe yupingfeng keli zhiliao changnianxing bianyingxing biyan]. *Chinese Journal of Otorhinolaryngology of Integrated Traditional and Western Medicine] [Zhongguo Zhongxiyi Jiehe Erbiyanhouke Zazhi], 12*(4), 193-194.

Chen, L., & Chen, X. W. (2014). Analysis on therapeutic effect of Cetirizine combined with Yupingfengsan in treating allergic rhinitis [Xitiliqin lianhe Yupingfengsan zhiliao guominxing biyan liaoxiao fenxi]. *World Chinese Medicine, 9*(7), 880-882.

Chen, L. L. (2013). *Kinetics of testing and toxicokinetics Xanthium toxic components.* (Masters), Guangzhou University of Chinese Medicine. Available from Cnki

Chen, M. H., Su, T. P., Chen, Y. S., Hsu, J.-W., Huang, K. L., Chang, W. H., & Bai, Y. M. (2013). Allergic rhinitis in adolescence increases the risk of depression in later life: A nationwide population-based prospective cohort study. *Journal of Affective Disorders, 145*(1), 49-53.

Chen, N., Wu, Q. C., Chi, G. F., Soromou, L. W., Hou, J. L., Deng, Y. H., & Feng, H. H. (2013). Prime-O-glucosylcimifugin attenuates lipopolysaccharide-induced acute lung injury in mice. *International Immunopharmacology, 16*(2), 139-147.

Chen, S. M. (2014). Astragalus membranaceus modulates Th1/2 immune balance and activates PPAR [gamma] in a murine asthma model. *Biochemistry and Cell Biology, 92*(5).

Chen, W. X. (2009). *Influence from long term toxicity of Asarum on renal function and renal morphology of SD rats.* (Masters), Hubei University of Chinese Medicine, Hubei, China.

Chen, Y. T., & Chen, G. Q. (2011). Jiawei Yupingfengsan with budesonide nasal spray in the treatment of 46 allergic rhinitis cases[Jiawei Yupingfengsan peihe budinaide bipenwuji zhiliao bianyingxing biyan 46 li]. *Shaanxi Journal of Traditional Chinese Medicine [Shaanxi Zhongyi], 32*(7).

Chiang, S.Y., Lee, P.Y., Lai, M.T., Shen, L.C., Chung, W.S., Huang, H.F., . . . Wu, H.C. (2011). Safrole-2′,3′-oxide induces cytotoxic and genotoxic effects in HepG2 cells and in mice. *Mutation Research/Genetic Toxicology and Environmental Mutagenesis, 726*(2), 234-241.

Chin, Y. W., Jung, Y. H., Chae, H. S., Yoon, K. D., & Kim, J. W. (2011). Anti-inflammatory constituents from the roots of Saposhnikovia divaricata. *Bulletin of the Korean Chemical Society, 32*(6), 2132-2134.

China Medicinal Herb Suppliers. (2010). Buffaloes' horns [Shuiniu Jiao]. In C. M. H. S. Z. y. shichang] (Ed.), (Vol. 640x480). Bozhou, Anhui, China: zgycsc@163.com.

Chinese Pharmacopoeia Commission. (2015). *Pharmacopoeia of People's Republic of China [Zhongguoyaodian]* (15th ed. Vol. 1). Beijing, China: Medico-Pharmacuetical Science & Technology.

Choi, Y. K., Cho, G. S., Hwang, S. Y., Kim, B. W., Lim, J. H., Lee, J. C., . . . Kim, Y. S. (2010). Methyleugenol reduces cerebral ischemic injury by suppression of oxidative injury and inflammation. *Free Radical Research, 44*(8), 925-935.

Chon, T. Y. M. D., & Lee, M. C. M. D. (2013). Acupuncture. *Mayo Clinic Proceedings, 88*(10), 1141-1146.

Chui, S. H., Shek, S. L., Szeto, Y. T. & Chan, K. (2010) A panel study to evaluate quality of life assessments in patients suffering from allergic rhinitis after treatment with a Chinese herbal nasal drop. *Pythotherapy Research, 24*, 609-613.

Ciprandi, G., Signori, A., Tosca, M. A., & Cirillo, I. (2011). Spirometric abnormalities in patients with allergic rhinitis: Indicator of an "asthma march"? *American Journal of Rhinology & Allergy, 25*(5), 181-185.

Colás, C., Galera, H., Añibarro, B., Soler, R., Navarro, A., Jáuregui, I., & Peláez, A. (2012). Disease severity impairs sleep quality in allergic rhinitis (The SOMNIAAR study). *Clinical and Experimental Allergy: Journal of the British Society for Allergy and Clinical Immunology, 42*(7), 1080-1087.

Compalati, E., & Ridolo, E. (2010). The link between allergic rhinitis and asthma: The united airways disease. *Expert Review of Clinical Immunology, 6*(3), 413-423.

Crown, E. D., Ye, Z. M., Johnson, K. M., Xu, G. Y., McAdoo, D. J., & Hulsebosch, C. E. (2006). Increases in the activated forms of ERK 1/2, p38 MAPK, and CREB are correlated with the expression of at-level mechanical allodynia following spinal cord injury. *Experimental Neurology*, *199*(2), 397-407.

Curtis, L., Lieberman, A., Stark, M., Rea, W., & Vetter, M. (2004). Adverse health effects of indoor molds. *Journal of Nutritional and Environmental Medicine*, *14*(3), 261-274.

D'Amato, G., Bergmann, K. C., Cecchi, L., Annesi-Maesano, I., Sanduzzi, A., Liccardi, G., . . . D'Amato, M. (2014). Climate change and air pollution: Effects on pollen allergy and other allergic respiratory diseases. *Allergo Journal International*, *23*(1), 17-23.

D'Amato, G., Holgate, S. T., Pawankar, R., Ledford, D. K., Cecchi, L., Al-Ahmad, M., . . . Annesi-Maesano, I. (2015). Meteorological conditions, climate change, new emerging factors, and asthma and related allergic disorders. A statement of the World Allergy Organization. *World Allergy Organization Journal*, *8*(1), 25.

Dai, J. N., Chen, X. H., Cheng, W. M., Liu, X., Fan, X., Shen, Z. D., & Bi, K. S. (2008). A sensitive liquid chromatography–mass spectrometry method for simultaneous determination of two active chromones from Saposhnikovia root in rat plasma and urine. *Journal of Chromatography B*, *868*(1–2), 13-19.

Dallongeville, A., Le Cann, P., Zmirou-Navier, D., Chevrier, C., Costet, N., Annesi-Maesano, I., & Blanchard, O. (2015). Concentration and determinants of molds and allergens in indoor air and house dust of French dwellings. *Science of the Total Environment*, *536*, 964-972.

Dazaley, P. (2015). 9 things you probably didn't know about sneezing. Retrieved from http://www.huffingtonpost.com/2014/03/14/sneezing-facts-didnt-know_n_4936611.html. Accessed 31 May 2015.

de la Hoz Caballer, B., Rodriguez, M., Fraj, J., Cerecedo, I., Antolin-Amerigo, D., & Colas, C. (2012). Allergic rhinitis and its impact on work productivity in primary care practice and a comparison with other common diseases: The cross-sectional study to evaluate work productivity in allergic rhinitis compared with other common dIseases (CAPRI) study. *American Journal of Rhinology Allergy*, *26*(5), 390-394.

Deifl, S., & Bohle, B. (2011). Factors influencing the allergenicity and adjuvanticity of allergens. *Immunotherapy*, *3*(7), 881-893.

Derebery, J. M., Meltzer, E. O., & Boyle, J. M. (2008). Nasal allergies adversely affect sleep and productivity in children. *Annals Of Allergy Asthma & Immunology*, *100*(1), A3.

Drew, A. K., Whyte, I. M., Bensoussan, A., Dawson, A. H., Zhu, X., & Myers, S. P. (2002). Chinese herbal medicine toxicology database: Monograph on Herba Asari, "xi xin". *Clinical toxicology*, *40*(2), 169-172.

Eifan, A. O., Akkoc, T., Yildiz, A., Keles, S., Ozdemir, C., Bahceciler, N. N., & Barlan, I. B. (2010). Clinical efficacy and immunological mechanisms of sublingual and subcutaneous immunotherapy in asthmatic/rhinitis children sensitized to house dust mite: An open randomized controlled trial. *Clinical and Experimental Allergy*, *40*(6), 922-932.

Erekosima, N., Suarez-Cuervo, C., Ramanathan, M., Kim, J. M., Chelladurai, Y., Segal, J. B., & Lin, S. Y. (2014). Effectiveness of subcutaneous immunotherapy for allergic rhinoconjunctivitis and asthma: A systematic review. *The Laryngoscope*, *124*(3), 616-627.

Gao, Y. (2009). *The effect of Poria, Cinnamon Twig, Ovate Atractylodes, and Liarice decoction on quality of life of patients with perennial allergic rhinitis [Lingguizhugantang jiawei zhiliao changnianxing bianyingxing biyan de liaoxiao guancha ji dui huanzhe shenghuo zhiliang de yingxiang]*. (Masters), Chengdu University of Traditional Chinese Medicine [Chengdu Zhongyiyao Daxue] Chengdu, China.

Gevaert, P., Nouri-Aria, K. T., Wu, H., Harper, C. E., Takhar, P., Fear, D. J., . . . Gould, H. J. (2013). Local receptor revision and class switching to IgE in chronic rhinosinusitis with nasal polyps. *Allergy*, *68*(1), 55-63.

Global Alliance against Chronic Respiratory Diseases. (2007). *Global surveillance, prevention and control of chronic respiratory diseases a comprehensive approach* Bousquet. J. & N. Khaltaev (Eds.), (pp. 1-129). Retrieved from http://www.who.int/gard/publications/en/ . Accessed 27 Oct 2015.

Greiner, A. N., Hellings, P. W., Rotiroti, G., & Scadding, G. K. (2012). Allergic rhinitis. *The Lancet*, *378*(9809), 2112-2122.

Greisner, W. A., III, Settipane, R. J., & Settipane, G. A. (2000). The course of asthma parallels that of allergic rhinitis: A 23-year follow-up study of college students. *Allergy and Asthma Proceedings, 21*(6), 371-375.

Grollman, A. P. (2013). Aristolochic acid nephropathy: Harbinger of a global iatrogenic disease. *Environmental and Molecular Mutagenesis, 54*(1), 1-7.

Gu, D. M., Lu, P. H., Zhang, K., Wang, X., Sun, M., Chen, G. Q., & Wang, Q. (2015). EGFR mediates astragaloside IV-induced Nrf2 activation to protect cortical neurons against in vitro ischemia/reperfusion damages. *Biochemical and Biophysical Research Communications, 457*(3), 391-397.

Gu, X. P. (2016). Goat's Lungs [Yang Fei]. In b. c. S. Baike] (Ed.), (Vol. 300x212). China.

Guo, R. L., Pittler, M. H., & Ernst, E. (2007). Herbal medicines for the treatment of allergic rhinitis: A systematic review. *Annals of Allergy, Asthma & Immunology, 99*(6), 483-495.

Guo, J. F., Zhao, Z., & Kong, Q. (2010). Clinical effects of allergic rhinitis with Qufeng zhiyang koufuye [Qufeng zhiyang koufuye zhiliao guominxing biyan liaoxiao guancha]. *Hubei Journal of Traditional Chinese Medicine [Hubei Zhongyi Zazhi], 32*(10), 24-25.

Gupta, R., Sheikh, A., Strachan, D. P., & Anderson, H. R. (2004). Burden of allergic disease in the UK: Secondary analyses of national databases. *Clinical & Experimental Allergy, 34*(4), 520-526.

Han H. Y., & Wang, D. H. (2002). Long term effects of kidney tonifying and warming lung capsule for the treatment of allergic rhinitis [Bushenwenfei jiaonang zhiliao guominxing biyan de yuanqi liaoxiao guancha]. *Chinese Journal of Otorhinolaryngology of Integrated Traditional and Western Medicine [Zhongguo Zhongxiyi Jiehe Erbiyanhouke Zazhi], 10*(5), 233-234.

Hernandez-Trujillo, V. (2009). Antihistamines treatment for allergic rhinitis: different routes, different mechanisms? *Allergy and Asthma Proceedings, 30*(6), 584-588.

Higgins, J. P. T., & Green, S. e. (2011). *Cochrane Handbook for Systemic Reviews of Interventions Version 5.1.0 [updated March 2011]*. England: The Cochrane Collaboration, 2011

Hong, W., Liu, A. H., Hong, Y., & Fang, Z. W. (2005). Clinical study of compounds for allergic rhinitis [Fufang biyantang zhiliao bianyingxing biyan de linchuang yanjiu]. *Practical Clinical Journal of Integrated Traditional Chinese and Western Medicine [Shiyong Zhongxiyi Jiehe Linchuang], 5*(5), 41-42.

Hu, G., & Walls, R. S. (2005). Traditional Chinese medicine in the management of allergic diseases: An increasing trend. *Allergy & Clinical Immunology International, 17*(3), 88-96.

Hu, R. (2015). Encyclopaedia of traditional Chinese medicine [Zhong Hua Yi Dian]. Changsha: Hunan Electronic and Audio-Visual Publishing House

Hu, G., Walls, R. S., Bass, D., Ramon, B., Grayson, D., Jones, M., & Gebski, V. (2002). The Chinese herbal formulation Biminne in management of perennial allergic rhinitis: A randomized, double-blind, placebo-controlled, 12-week clinical trial. *Annals of Allergy, Asthma & Immunology, 88*(5), 478-487.

Huang, G. F. (2008). Impact of Wenfeizhiliu pills for perennial allergic rhinitis sufferers in peripheral blood IL4 and IFN-r [Wenfeizhiliudan dui changnianxing bianyingxing biyan huanzhe xueqing IL-4, IFN-r de yingxiang]. *Jilin Journal of Traditional Chinese Medicine [Jilin Zhongyi Yao], 28*(12), 884-885.

Huang, M. H., Wang, B. S., Chiu, C. S., Amagaya, S., Hsieh, W. T., Huang, S. S., . . . Huang, G. J. (2011). Antioxidant, antinociceptive, and anti-inflammatory activities of Xanthii Fructus extract. *Journal of Ethnopharmacology, 135*(2), 545-552.

Huang, P., Yu, Y. B., & Ma, Z. X. (2010). Clinical study on "Jiemin Qufeng Decoction II" in treating allergic rhinitis [Jiemin qufeng erhaofang zhiliao bianyingxing biyan linchuang yanjiu]. *Shanghai Journal of Traditional Chinese Medicine [Shanghai Zhongyiyao Zazhi], 44*(3), 32-34.

Huang, Z. Y. (2006). Bimin nasal irrigation for the treatment of 71 cases of allergic rhinitis [Biminshui zhiliao biantai fanyingxing biyan 71 li]. *Guangxi Journal of Traditional Chinese Medicine [Guangxi Zhongyi Yao], 29*(2), 21-22.

IBM Corp. (2015). IBM SPSS Statistics for windows (Version 23). Armonk, NY: IBM Corp.

Ichinose, T., Hiyoshi, K., Yoshida, S., Takano, H., Inoue, K., Nishikawa, M., . . . Shibamoto, T. (2009). Asian sand dust aggravates allergic rhinitis in guinea pigs induced by Japanese cedar pollen. *Inhalation Toxicology, 21*(12), 985-993.

Ichinose, T., Yoshida, S., Hiyoshi, K., Sadakane, K., Takano, H., Nishikawa, M., . . . Shibamoto, T. (2008). The effects of microbial materials adhered to Asian sand dust on allergic lung inflammation. *Archives of Environmental Contamination and Toxicology, 55*(3), 348-357. doi:

Jarvinen, T. A. H., & Liu, E. T. (2003). HER-2/neu and topoisomerase IIalpha] in breast cancer. *Breast Cancer Research and Treatment, 78*(3), 299-311.

Jenmalm, M. C., & Björkstén, B. (2016). Microbiome and the effect on immune response In H. A. Sampson (Ed.), *Allergy, Immunity and Tolerance in Early Childhood* (pp. 171-194). Amsterdam: Academic Press.

Jiang, Z. J. (1997). Clinical effects of Yufengjianbitang in perennial allergic rhinitis [Yufengjianbitang zhiliao changnianxing bianyingxing biyan liaoxiao guancha. *Chinese Journal of Primary Medicine [Zhongguo Ji Ceng Yixue], 4*(4), 36-37.

Jin, H. M. (2010). Clinical observation of Kemin decoction in treating perennial allergic rhinitis [Kemintang zhiliao changnianxing bianyingxing biyan linchuang guancha]. *Chinese Journal of Traditional Chinese Medicine and Pharmacy [Zhonghua Zhongyiyao Zazhi], 25*(12), 2192-2193.

Jin, M., Kijima, A., Hibi, D., Ishii, Y., Takasu, S., Matsushita, K., . . . Umemura, T. (2013). In vivo genotoxicity of methyleugenol in gpt delta transgenic rats following medium-term exposure. *Toxicological Sciences, 131*(2), 387-394.

Jin, M., Kijima, A., Suzuki, Y., Hibi, D., Inoue, T., Ishii, Y., . . . Umemura, T. (2011). Comprehensive toxicity study of safrole using a medium-term animal model with gpt delta rats. *Toxicology, 290*(2–3), 312-321.

Jung, H. W., Jung, J.-K., Cheong, W. C., Kang, J.-S., & Park, Y.-K. (2012). Antiallergic effect of KOB03, a polyherbal medicine, on mast cell-mediated allergic responses in ovalbumin-induced allergic rhinitis mouse and human mast cells. *Journal of Ethnopharmacology, 142*(3), 684-693.

Jung, J. W., Kang, H. R., Ji, G. E., Park, M. S., Song, W. J., Kim, M. H., . . . Min, K. U. (2011). Therapeutic effects of fermented red ginseng in allergic rhinitis: A randomized, double-blind, placebo-controlled study. *Allergy, Asthma & Immunology Research, 3*(2), 103-110.

Kao, S. T., Lin, C. S., Hsieh, C. C., Hsieh, W. T., & Lin, J. G. (2001). Effects of xiao-qing-long-tang (XQLT) on bronchoconstriction and airway eosinophil infiltration in ovalbumin-sensitized guinea pigs: in vivo and in vitro studies. *Allergy, 56*(12), 1164-1171.

Kasaian, M. T., Marquette, K., Fish, S., DeClercq, C., Agostinelli, R., Cook, T. A., . . . Tchistiakova, L. (2013). An IL-4/IL-13 dual antagonist reduces lung inflammation, airway hyperresponsiveness, and IgE production in mice. *American Journal of Respiratory Cell and Molecular Biology (Online), 49*(1), 37-46.

Kellner, U., Maxwell, S., Jensen, P. B., Gieseler, F., & Rudolph, P. (2002). Culprit and victim - DNA topoisomerase II. *Lancet Oncology, 3*(4), 235-243.

Kern, J., & Bielory, L. (2014). Complementary and alternative therapy (CAM) in the treatment of allergic rhinitis. *Current Allergy and Asthma Reports, 14*(12), 1-6.

Khan, S., Shehzad, O., Chun, J. M., & Kim, Y. S. (2013). Mechanism underlying anti-hyperalgesic and anti-allodynic properties of anomalin in both acute and chronic inflammatory pain models in mice through inhibition of NF-κB, MAPKs and CREB signaling cascades. *European Journal of Pharmacology, 718*(1–3), 448-458.

Khan, S., Shin, E. M., Choi, R. J., Jung, Y. H., Kim, J., Tosun, A., & Kim, Y. S. (2011). Suppression of LPS-induced inflammatory and NF-κB responses by anomalin in RAW 264.7 macrophages. *Journal of Cellular Biochemistry, 112*(8), 2179-2188.

Kim, A. R., Choi, J. Y., Kim, J. I., Jung, S. Y., & Choi, S. M. (2011). Acupuncture treatment of a patient with persistent allergic rhinitis complicated by rhinosinusitis and asthma. *Evidence-Based Complementary and Alternative Medicine, 2011*, 5.

Kim, S. Y., Kang, I. H., Nam, J. B., Cho, Y. C., Chung, D. Y., Kim, S. H., . . . Shin, J. W. (2015). Ameliorating the effect of astragaloside IV on learning and memory deficit after chronic cerebral hypoperfusion in rats. *Molecules, 20*(2), 1904-1921.

Kong, X. Y., Liu, C. F., Zhang, C., Zhao, J., Wang, J. Z., Wan, H. Y., . . . Lin, N. (2013). The suppressive effects of Saposhnikovia divaricata (Fangfeng) chromone extract on rheumatoid arthritis via inhibition of nuclear factor-κB and mitogen activated proteinkinases activation on collagen-induced arthritis model. *Journal of Ethnopharmacology, 148*(3), 842-850.

Kramer, A., Bekeschus, S., Bröker, B. M., Schleibinger, H., Razavi, B., & Assadian, O. (2013). Maintaining health by balancing microbial exposure and prevention of infection: The hygiene

hypothesis versus the hypothesis of early immune challenge. *Journal of Hospital Infection, 83*, S29-S34.

Kreiner, J., Pang, E., Lenon, G., & Yang, A. W. H. (2016). Saposhnikoviae divaricata: A phytochemical, pharmacological and pharmakinetic review. *Chinese Journal of Natural Medicines* (accepted on May 30 2016).

Kuan, Z. (2011). *Pharmacological studies VOMbp anti-allergic rhinitis.* (Masters), Zhejiang University of Traditional Chinese Medicine, ZheJiang, China.

Kuo, Y. C., Lin, Y. L., Huang, C. P., Shu, J. W., & Tsai, W. J. (2002). A tumor cell growth inhibitor from Saposhnikovae divaricata. *Cancer Invest, 20*(7-8), 955-964.

Laumbach, R. J., & Kipen, H. M. (2012). Respiratory health effects of air pollution: Update on biomass smoke and traffic pollution. *Journal of Allergy and Clinical Immunology, 129*(1), 3-11.

Lee, K., Chung, D., Shin, S., Kim, S., & Cho, J. (2008). Stress and fatigue in allergic rhinitis patients. *Journal of Allergy and Clinical Immunology, 121*(2, Supplement 1), S130.

Lee, M. H., Yang, Y. Y., Tsai, Y. H., Lee, Y. L., Huang, P. Y., Huang, I. J., . . . Leu, S. J. (2008). The effect of Chinese herbal medicines on TNF-α induced matrix metalloproteinase-1, -9 activities and interleukin-8 secretion. *Botanical Studies, 49*(4), 301-309.

Léger, D., Annesi-Maesano, I., Carat, F., Rugina, M., Chanal, I., Pribil, C., . . . Bousquet, J. (2006). Allergic rhinitis and its consequences on quality of sleep: An unexplored area. *Archives of internal medicine, 166*(16), 1744-1748.

Lenon, G. B., Li, C. G., Da Costa, C., Thien, F. C. K., Shen, Y., & Xue, C. C. L. (2012). Lack of efficacy of a herbal preparation (RCM-102) for seasonal allergic rhinitis: a double blind, randomised, placebo-controlled trial. *Asia Pacific Allergy, 2*(3), 187-194.

Lenon, G. B., Li, C. G., Xue, C. C. L., Thien, F. C. K., & Story, D. F. (2008). Inhibition of inducible nitric oxide production and iNOS protein expression in lipopolysaccharide-stimulated rat aorta and Raw 264.7 macrophages by ethanol extract of a Chinese herbal medicine formula (RCM-101) for allergic rhinitis. *Journal of Ethnopharmacology, 116*(3), 547-553.

Lenon, G. B., Xue, C. C. L., Story, D. F., Thien, F. C. K., McPhee, S., & Li, C. G. (2007). Inhibition of release of inflammatory mediators in primary and cultured cells by a Chinese herbal medicine formula for allergic rhinitis. *Chinese Medicine, 2*, 1-8.

Leung, T. F., Ko, F. W. S., & Wong, G. W. K. (2012). Roles of pollution in the prevalence and exacerbations of allergic diseases in Asia. *Journal of Allergy and Clinical Immunology, 129*(1), 42-47.

Leynaert, B., Neukirch, C., Liard, R., Bousquet, J., & Neukirch, F. (2000). Quality of life in allergic rhinitis and asthma. A population-based study of young adults. *American Journal of Respiratory and critical care medicine, 162*(4 Pt 1), 1391-1396.

Li, F., Zhou, Y., Li, S., Jiang, F., Jin, X., Yan, C., . . . Shen, X. (2011). Prevalence and risk factors of childhood allergic diseases in eight metropolitan cities in China: A multicenter study. *BMC Public Health, 11*(1), 1-9.

Li, J., Zhang, Y., & Zhang, L. (2015). Discovering susceptibility genes for allergic rhinitis and allergy using a genome-wide association study strategy. *Current Opinion in Allergy Clinical Immunology, 15*(1), 33-40.

Li, J. J. (2007). *[The impact of long-term toxicity of Asarum SD rat liver tissue morphology and liver function]*. (Masters), Hubei University of Chinese Medicine, Hubei, China.

Li, L., Li, B., Zhang, H. R., Zhao, A. Q., Han, B. H., Liu, C. M., & Tsao, R. (2015). Ultrafiltration LC-ESI-MSn screening of MMP-2 inhibitors from selected Chinese medicinal herbs Smilax glabra Roxb., Smilax china L. and Saposhnikovia divaricata (Turcz.) Schischk as potential functional food ingredients. *Journal of Functional Foods, 15*, 389-395.

Li, Q. L. (2012). Differential treatment of 52 cases of allergic rhinitis [Bianzheng zhiliao guominxing biyan 52 li liaoxiao guancha]. *Zhejiang Chinese Medicine Journal [Zhejiang Zhongyi Zhazhi], 47*(10), 717-718.

Li, R. (2012). Integrated Chinese medicine and Western medicine for the treatment of 80 cases of children with allergic rhinitis [Zhongxiyao jiehe zhiliao erdong guominxing biyan 80 li liaoxiao guancha]. *Chinese Journal of Clinical Rational Drug Use [Linchuang Heli Yongyao], 5*(4), 69.

Li, R. R., Yang, Y., Ding, J. X., Qin, C., & Li, J. (2012). Experimental comparison study on mice's acute toxicity of different composition in Asarum. *Chinese Journal of Pharmacovigilance, 9*(06), 321-324.

Li, S. L. (2008). Clinical efficacy of combined Chinese medicine and Western medicine for 30 cases of allergic rhinitis [Zhongxiyi jiehe zhiliao bianyingxing biyan 30 li linchuang guancha]. *Guiding Journal of TCM [Zhongyi Zhidao Bao], 3*, 50-53.

Liang, S. Q. (2011). Clinical observation of modified Spleen qi deficiency Buzhongyiqitang for the treatment of perennial allergic rhinitis [Jiawei buzhongyizitang zhiliao feiqiquxing changnianxing bianyingxing biyan de linchuang zhiliao guanzha]. *China Health Industry [Zhongyi Weisheng Chanye], 8*(5), 100-101.

Lin, S. (2013). Clinical observation on 60 cases of children with allergic rhinitis treated by integrative medicine [Zhongxiyi jiehe zhiliao xiaoer guominxing biyan 60 li linchuang guancha]. *Fujian Journal of Traditional Chinese Medicine, 44*(2), 14-15.

Linneberg, A., Henrik Nielsen, N., Frølund, L., Madsen, F., Dirksen, A., & Jørgensen, T. (2002). The link between allergic rhinitis and allergic asthma: A prospective population-based study. The Copenhagen Allergy Study. *Allergy, 57*(11), 1048-1052.

Liu, G., & Song, R. H. (2004). A clinical observation on the therapeutic effects of a combined therapy with dibiling nose dropping and septum rectifying operation on allergic rhinitis [Dibiling peihe shoushu jiaozheng bizhongge pianqu zhiliao bianyingxing biyan de linchuang guancha]. *Chinese Journal of Otorhinolaryngology of Integrated Traditional and Western Medicine [Zhongguo Zhongxiyi Jiehe Erbiyanhouke Zazhi], 12*(1), 20-21.

Liu, H., Tian, J. M., Sun, L., Bai, X. M., Li, X. J., & Jia, T. J. (2008). [Reactions of macrophage and lymphocyte subsets in normal mice to Radix Saposhnikoviae polysaccharide]. *Journal of Clinical Rehabilitative Tissue Engineering Research, 12*(18), 3475-3478.

Liu, Q. P., Liu, J. H., Li, Y. L., & Ge, Y. H. (2001). Nourishing Liver Yin in the treatment of allergic rhinitis [Yangyin pingganfa zhiliao biantai fanyingxing biyan]. *Journal of Beijing University of Traditional Chinese Medicine [Beijing Zhongyiyao Daxue Xuebao], 24*(2), 68-69.

Liu, Y., Gao, H., Wang, Z., & Zhang, Q. (2010). [Trace analysis of aristolochic acid A]. *Zhongguo Zhong Yao Za Zhi, 35*(24), 3314-3317.

Livingston, A., & Drape, J. (2016, 30 Nov). Vic Asthma thunderstorm was the world's worst. *Australian Associated Press*. Retrieved from http://www.news.com.au/national/breaking-news/asthma-warning-ahead-of-victorian-storms/news-story/86571958e4f92127e73c8516706b618c. Accessed 30 Nov 2016.

Lu, B., Chang, K., Wang, H. J., Guo, J. J., & Chen, J. (2011). Regulating Ying and Wei in the treatment of 60 allergic rhinitis cases [Tiaohe yingweifa zhiliao guominxing biyan 60 li liaoxiao guancha]. *Shanxi Journal of Traditional Chinese Medicine [Shanxi Zhongyi], 27*(3), 10-11.

Lu, B. Q., Sun, Y. F., Guo, Y. L., Xu, Q. W., & Zhou, X. J. (2003). A clinical observation on the therapeutic effects of a combined therapy with nasonex and bimin formula on allergic rhinitis [Neishuna bipenwuji lianhe zhongyao biminfang zhiliao bianyingxing biyan de linchuang guancha]. *Chinese Journal of Otorhinolaryngology of Integrated Traditional and Western Medicine [Zhongguo Zhongxiyi Jiehe Erbiyanhouke Zazhi], 11*(6), 272-274.

Lu, J. (1999). *The complete collection of traditional texts on Chinese materia medica [Zhong Guo Ben Cao Quan Shu]* (1st ed.). Beijing: Huaxia Publishing House.

Lu, J. (2009). Observation of Chinese and Western medicine for the treatment of 30 cases of perennial allergic rhinitis [Zhongxiyao heyong changnianxing bianyingxing biyan 30 li guancha]. *Journal of Practical Traditional Chinese Medicine [Shiyong Zhongyiyao Zazhi], 25*(6), 380-381.

Lu, P., Shi, Y. M., & Xu, L. G. (1998). Integrative medicine clinical study of children with allergic rhinitis [Zhongxiyi jiehe zhiliao xiao'er guominxing biyan linchuang yanjiu]. *Chinese Journal of Integrated Traditional and Western Medicine [Zhongguo Zhongxiyi Jiehe Zazhi], 18*(7), 437.

Luo, G. W. (2013). Qingretongqiaotang self-limiting treatment of pediatric wind-heat type of allergic rhinitis [Zini Qingretongqiaosan zhiliao xiaoer feijing fengrexing guominxing biyan]. *Journal of Emergency in Traditional Chinese Medicine [Zhongguo Zhongyi Jizhen], 22*(12), 2095-2096.

MacGlashan Jr, D. (2008). IgE receptor and signal transduction in mast cells and basophils. *Current Opinion in Immunology, 20*(6), 717-723.

Maciocia, G. (2008). *The foundations of Chinese medicine* (Second ed.). Philadelphia, USA.: Churchill Livingstone.Elsevier Ltd.

Maftouh, M., Avan, A., Sciarrillo, R., Granchi, C., Leon, L. G., Rani, R., . . . Giovannetti, E. (2014). Synergistic interaction of novel lactate dehydrogenase inhibitors with gemcitabine against pancreatic cancer cells in hypoxia. *British Journal of Cancer, 110*(1), 172-182.

Mahmudi-Azer, S., Downey, G. P., & Moqbel, R. (2002). Translocation of the tetraspanin CD63 in association with human eosinophil mediator release. *Blood, 99*(11), 4039-4047.

Mahr, T. A., Sheth, K. K., & Boyle, J. M. (2008). Lack of efficacy and bothersome effects decrease treatment adherence in children with allergic rhinitis. *Annals Of Allergy Asthma & Immunology, 100*(1), A3.

Marie-Hélène Dizier, Bouzigon, E., Guilloud-Bataille, M., Genin, E., Marie-Pierre Oryszczyn, Annesi-Maesano, I., & Demenais, F. (2007). Evidence for a locus in 1p31 region specifically linked to the co-morbidity of asthma and allergic rhinitis in the EGEA study. *Human Heredity, 63*(3-4), 162-167.

Matheson, M. C., Dharmage, S. C., Abramson, M. J., Walters, E. H., Sunyer, J., de Marco, R., . . . Svan es, C. (2011). Early-life risk factors and incidence of rhinitis: Results from the European Community Respiratory Health Study - an international population-based cohort study. *Journal of Allergy and Clinical Immunology, 128*(4), 816-823.

Matkovic, Z., Zivkovic, V., Korica, M., Plavec, D., Pecanic, S., & Tudoric, N. (2010). Efficacy and safety of Astragalus membranaceus in the treatment of patients with seasonal allergic rhinitis. *Phytotherapy Research, 24*(2), 175-181.

May, B. H., Lu, Y. B., Lu, C. J., Zhang, A. L., Chang, S. Y., & Xue, C. C. L. (2013). Systematic assessment of the representativeness of published collections of the traditional literature on Chinese medicine. *The Journal of Alternative & Complementary Medicine, 19*(5), 403-409.

McLeod, R. L., Erickson, C. H., Mingo, G. G., & Hey, J. A. (2001). Intranasal application of the alpha2-adrenoceptor agonist BHT-920 produces decongestion in the cat. *American Journal of Rhinology, 15*(6), 407-415.

Mehuys, E., Gevaert, P., Brusselle, G., van Hees, T., Adriaens, E., Christiaens, T., . . . Boussery, K. (2014). Self-medication in persistent rhinitis: Overuse of decongestants in half of the patients. *Journal of Allergy and Clinical Immunology: In Practice, 2*(3), 313-319.

Meltzer, E. O., Blaiss, M. S., Naclerio, R. M., Stoloff, S. W., Derebery, M. J., Nelson, H. S., . . . Wingertzahn, M. A. (2012). Burden of allergic rhinitis: Allergies in America, Latin America, and Asia-Pacific adult surveys. *Allergy and Asthma Proceedings, 33 Suppl 1*, S113-S141.

Meltzer, E. O., & Bukstein, D. A. (2011). The economic impact of allergic rhinitis and current guidelines for treatment. *Annals of allergy, asthma & immunology: Official Publication of the American College of Allergy, Asthma, & Immunology, 106*(2 Suppl), S12-S16.

Millot, S., Andrieu, V., Letteron, P., Lyoumi, S., Hurtado-Nedelec, M., Karim, Z., . . . Beaumont, C. (2010). Erythropoietin stimulates spleen BMP4-dependent stress erythropoiesis and partially corrects anemia in a mouse model of generalized inflammation. *Blood, 116*(26), 6072-6081.

Mitchell, P. D. (2011). Retrospective diagnosis and the use of historical texts for investigating disease in the past. *International Journal of Paleopathology, 1*(2), 81-88.

Moghadam-Kia, S., & Werth, V. P. (2010). Prevention and treatment of systemic glucocorticoid side effects. *International Journal of Dermatology, 49*(3), 239-248.

Nagai, T., Arai, Y., Emori, M., Nunome, S.-y., Yabe, T., Takeda, T., & Yamada, H. (2004). Anti-allergic activity of a Kampo (Japanese herbal) medicine "Sho-seiryu-to (Xiao-Qing-Long-Tang)" on airway inflammation in a mouse model. *International Immunopharmacology, 4*(10–11), 1353-1365.

Nathan, R. A. (2007). The burden of allergic rhinitis. *Allergy and Asthma Proceedings, 28*(1), 3-9.

Nonlinear Dynamics. (2016). Correlation Analysis Retrieved from http://www.nonlinear.com/support/progenesis/comet/faq/v2.0/dendrogram.aspx. Accessed September 2016.

Norback, D., Lampa, E., & Engvall, K. (2014). Asthma, allergy and eczema among adults in multifamily houses in Stockholm (3-HE study) -associations with building characteristics, home environment and energy use for heating. *PLoS One, 9*(12), e112960.

Novelli, F., Malagrinò, L., Dente, F. L., & Paggiaro, P. (2012). Efficacy of anticholinergic drugs in asthma. *Expert Review of Respiratory Medicine, 6*(3), 309-319.

Oka, A., Matsunaga, K., Kamei, T., Sakamoto, Y., Hirano, T., Hayata, A., . . . Yamamoto, N. (2014). Ongoing allergic rhinitis impairs asthma control by enhancing the lower airway inflammation. *Journal of Allergy and Clinical Immunology: In Practice, 2*(2), 172-178.

Okuyama. E., Hasegawa. T., Masushita, T., Fujimoto, H., Ishibashi, M., & Yamazaki, M. (2001). Analgesic components of saposhnikovia root Saposhnikovia divaricata. *Chemical & Pharmaceutical Bulletin, 49*(Suppl 2).

Osguthorpe, J. D. (2013). Pathophysiology of and potential new therapies for allergic rhinitis. *International Forum of Allergy & Rhinology, 3*(5), 384-392.
Ozdoganoglu, T., & Songu, M. (2012). The burden of allergic rhinitis and asthma. *Therapeutic Advances in Respiratory Disease, 6*(1), 11-23.
Park, C., Shin, S., Lee, K., Cho, J., & Kim, S. (2012). The effect of allergic rhinitis on the degree of stress, fatigue and quality of life in OSA patients. *European Archives of Oto-Rhino-Laryngology, 269*(9), 2061-2064.
Patridge, E., Gareiss, P., Kinch, M. S., & Hoyer, D. (2016). An analysis of FDA-approved drugs: natural products and their derivatives. *Drug Discovery Today, 21*(2), 204-207.
Pawankar, R., Bunnag, C., Chen, Y. Z., Fukuda, T., You-Young, K., Lan Thi Tuyet, L., . . . Bousquet, J. (2009). Allergic rhinitis and its impact on asthma update (ARIA 2008) - Western and Asian-Pacific perspective. *Asian Pacific Journal of Allergy and Immunology, 27*(4), 237-243.
Pawankar, R., Canonica, G. W., Holgate, S. T., & Lockey, F. L. E. (2011). *WAO white book on allergy*. United States of America: World Allergy Organization.
Pawankar, R., Canonica, G. W., Holgate, S. T., & Lockey, R. F. (2012). Allergic diseases and asthma: a major global health concern. *Current Opinion in Allergy and Clinical Immunology, 12*(1).
Pawankar, R., Mori, S., Ozu, C., & Kimura, S. (2011). Overview on the pathomechanisms of allergic rhinitis. *Asia Pacific Allergy, 1*(3), 157-167.
Peng, S. L., Zhong, Q. & Huang, Q. S. (2001). Clinical observation of Biminling treatment in 36 allergic rhinitis cases [Biminling zhiliao bianyingxing biyan 36 li linchuang guancha]. *Chinese Journal of Information on Traditional Chinese Medicine [Zhongguo Zhongyiyao Xinxi Zazhi], 8*(3), 58-59.
Peng, S. L., Zhong, Q. & Yuan, X. H. (2004). Clinical observation on 42 cases of perennial allergic rhinitis treated by Sheti Zhiqiu granules [Shetizhiqiu keli zhiliao changnianxing bianyingxing biyan 42 li linchuang guancha]. *Journal of Traditional Chinese Medicine [Zhongyi Zazhi], 45*(11), 836-837.
Pisoschi, A. M., & Pop, A. (2015). The role of antioxidants in the chemistry of oxidative stress: A review. *European Journal of Medicinal Chemistry, 97*, 55-74.
Portelli, M. A., Hodge, E., & Sayers, I. (2015). Genetic risk factors for the development of allergic disease identified by genome-wide association. *Clinical & Experimental Allergy, 45*(1), 21-31.
Pritchard, S. (2010). CHAPTER 1 - Foundations and development of Tui na *Tui Na* (pp. 3-14). Edinburgh: Churchill Livingstone.
Pudupakkam, K. V. (2014). Allergy skin testing In R. Katial (Ed.), *Textbook of allergy for clinician* (pp. 36-46): CRC Press.
Qin, H. (2006). *The study of the clinical curative effect of the traditional Chinese medicine Biyanyihao granule for infusion in the treatment of PAR [Zhongyao biyan yihao chongji zhiliao changnianxing bianyingxing biyan de linchuang yanjiu]*. (Masters), Heilongjiang University of Traditional Chinese Medicine [Heilongjiang Zhongyiyao Daxue], Heilongjiang, China.
Qiu, W. Y. (2012). *The allergic rhinitis TCM dialectical law and clinical research of Xiaoqinglong decoction treatment.* (Masters), Guangzhou University of Chinese medicine, Guangzhou, China.
Ramasamy, A., Curjuric, I., Coin, L. J., Kumar, A., McArdle, W. L., Imboden, M., . . . Jarvis, D. L. (2011). A genome-wide meta-analysis of genetic variants associated with allergic rhinitis and grass sensitization and their interaction with birth order. *Journal of Allergy and Clinical Immunology, 128*(5), 996-1005.
Ramey, J. T., Bailen, E., & Lockey, R. F. (2006). Rhinitis medicamentosa. *Journal of Investigational Allergology and Clinical Immunology, 16*(3), 148-155.
Raykov, T., & Marcoulides, G. A. (2012). *An Introduction to Applied Multivariate Analysis*. Hoboken: Taylor and Francis.
Rencher, A. C., & Christensen, W. F. (2012). *Methods of Multivariate Analysis* (3rd ed. ed.). Hoboken: Wiley.
Ricciardelli, L., Mellor, D., & McCabe, M. (2012). The quiet crisis: Challenges for men's health in Australia. *InPsych, 34*(4). Retrieved from https://www.psychology.org.au/inpsych/2012/august/ricciardelli/. Accessed Sept 2016.
Rietjens, I. M. C. M., Martena, M. J., Boersma, M. G., Spiegelenberg, W., & Alink, G. M. (2005). Molecular mechanisms of toxicity of important food-borne phytotoxins. *Molecular Nutrition & Food Research, 49*(2), 131-158.

Riveiro, M. E., De Kimpe, N., Moglioni, A., Vazquez, R., Monczor, F., Shayo, C., & Davio, C. (2010). Coumarins: old compounds with novel promising therapeutic perspectives. *Current Medical Chemistry, 17*(13), 1325-1338.

Robison, J. G., Pant, H., & Ferguson, B. J. (2010). Rhinitis medicamentosa as a cause of increased intraoperative bleeding. *The Laryngoscope, 120*(10), 2106-2107.

Rosenwasser, L. (2007). New insights into the pathophysiology of allergic rhinitis. *Allergy and Asthma Proceedings, 28*(1), 10-15.

Savolainen, J., Laaksonen, K., Rantio-Lehtimaki, A., & Terho, E. O. (2004). Increased expression of allergen-induced in vitro interleukin-10 and interleukin-18 mRNA in peripheral blood mononuclear cells of allergic rhinitis patients after specific immunotherapy. *Clinical & Experimental Allergy, 34*(3), 413-419.

Seidman, M. D., Gurgel, R. K., Lin, S. Y., Schwartz, S. R., Baroody, F. M., Bonner, J. R., . . . Nnacheta, L. C. (2015). Clinical practice guideline: Allergic rhinitis. *Otolaryngology - Head and Neck Surgery, 152*(1 suppl), S1-S43.

Shen, F., & Chen, X. N. (2004). Xiaofeng granule treatment of allergic rhinitis in 80 cases [Xiaofeng chongji zhiliao bianyingxing biyan 80 li]. *Liaoning Journal of Traditional Chinese Medicine [Liaoning Zhongyi Zazhi], 31*(1), 54.

Shi, H. Y., Zhuang, Y. & Wang, X. Y. (2014). Effect of Yupingfeng dropill in treatment of allergic rhinitis. *Chinese Journal Chinese Materia Medica, 29*(22), 105-106.

Shi, Q. Y., & Zhao, Y. (2012). The therapeutic effect of Xiangju capsule of perennial allergic rhinitis observation [Xiangju jiaonang zhiliao changnian guominxing biyan de liaoxiao guancha]. *Medical Innovation of China [Zhongguo yixue chuangxing], 9*(22), 105-106.

Sionneau, P. (1997). *Dui Yao: the art of combining Chinese medicinals*: Blue Poppy Enterprises, Inc.

Smurthwaite, L., & Durham, S. (2002). Local ige synthesis in allergic rhinitis and asthma. *Current Allergy and Asthma Reports, 2*(3), 231-238.

Sun, R. H. (2014). Clinical observation of treatment of Tongqiaobiyan capsules in allergic rhinitis [Tongqiaobiyan jiaonang zhiliao guominxing biyan de linchuang guancha]. *Guangming Traditional Chinese Medicine [Guangming Zhongyi], 29*(12), 2578-2588.

Taegtmeyer, A. B., Steurer-Stey, C., Spertini, F., Bircher, A., Helbling, A., Miedinger, D., . . . Leuppi, J. D. (2009). Allergic rhinitis in patients with asthma: The Swiss LARA (Link Allergic Rhinitis in Asthma) survey. *Current Medical Research & Opinion, 25*(5), 1073-1080.

Tai, J., & Cheung, S. (2007). Anti-proliferative and antioxidant activities of Saposhnikovia divaricata. *Oncology Reports, 18*(1).

Takeda, S., Noguchi, M., Matsuo, K., Yamaguchi, Y., Kudo, T., Nishimura, H., . . . Aramaki, H. (2013). (−)-Xanthatin up-regulation of the GADD45γ tumor suppressor gene in MDA-MB-231 breast cancer cells: Role of topoisomerase IIα inhibition and reactive oxygen species. *Toxicology, 305*, 1-9.

Takhar, P., Smurthwaite, L., Coker, H. A., Fear, D. J., Banfield, G. K., Carr, V. A., . . . Gould, H. J. (2005). Allergen drives class switching to IgE in the nasal mucosa in allergic rhinitis. *Journal of immunology (Baltimore, Md. : 1950), 174*(8), 5024-5032.

Tang, F., Chen, F. L., Ling, X., Huang, Y., Zheng, X. M., Tang, Q. F., & Tan, X. M. (2015). Inhibitory effect of Methyleugenol on IgE-mediated allergic inflammation in RBL-2H3 cells. *Mediators of Inflammation, 2015*, 9.

Tang, Y. Y., Song, K., Zeng. K.S. & Yang, M. F. (2008). Clinical observation on the therapeutic effects of supplemented four gentlemen decoction on perennial allergic rhinitis in the pattern of Spleen-Qi deficiency [Jiawei sijunzitang zhiliao piqixuxing changnianxing bianyingxing biyan de linchuang liaoxiao yanjiu]. *Chinese Journal of Otorhinolaryngology of Integrated Traditional and Western Medicine [Zhongguo Zhongxiyi Jiehe Erbiyanhouke Zazhi], 16*(6), 422-424.

The Cochrane Collaborations. (2014). Review Manager (RevMan) [Computer program] (Version 5.3.). Copenhagen: The Cochrane Collaboration

Therapeutic Goods Administration. (2001, 24 May). Aristolochia alert for practitioners. Retrieved from https://www.tga.gov.au/node/542. Accessed May 2015.

Theron, A. J., Steel, H. C., Tintinger, G. R., Gravett, C. M., Anderson, R., & Feldman, C. (2014). Cysteinyl leukotriene receptor-1 antagonists as modulators of innate immune cell function. *Journal of Immunology Research*.

Tobias, J. D., Cartabuke, R., & Taghon, T. (2014). Oxymetazoline (Afrin®): maybe there is more that we need to know. *Pediatric Anesthesia, 24*(8), 795-798. doi:10.1111/pan.12399

Tonelli, L. H., Katz, M., Kovacsics, C. E., Gould, T. D., Joppy, B., Hoshino, A., . . . Postolache, T. T. (2009). Allergic rhinitis induces anxiety-like behavior and altered social interaction in rodents. *Brain, Behavior, and Immunity, 23*(6), 784-793.

U.S. Food and Drug Administration. (1999). Additions to the list of drug products that have been withdrawn or removed from the market for reasons of safety or effectiveness. *Federal register, 65*(2). Retrieved from www.fda.gov/ohrms/dockets/ac/00/backgrd/3634b1a_tab1.pdf. Accessed Mar 2017.

Wagner, H., Bauer, R., Melchart, D., Xiao, P.-G., & Staudinger, A. E. (2011). *Chromatographic fingerprint analysis of herbal medicines thin layer and high performance liquid chromatography of Chinese drugs* Vol. 1. Retrieved from http://link.springer.com.ezproxy.lib.rmit.edu.au/book/10.1007/978-3-7091-0763-8/page/1. Accessed August 2016.

Walker, S. M., Durham, S. R., Till, S. J., Roberts, G., Corrigan, C. J., Leech, S. C., . . . Nasser, S. M. (2011). Immunotherapy for allergic rhinitis. *Clinical & Experimental Allergy, 41*(9), 1177-1200.

Wang, B. (1997). *Yellow emperor's canon of internal medicine* (L. S. Wu & Q. T. Wu, Trans.). Beijing, China: China Science & Technology Press.

Wang, D., & Clement, P. (1995). Assessment of early- and late-phase nasal obstruction in atopic patients after nasal allergen challenge. *Clinical Otolaryngology Allied Sciences, 20*(4), 368-373.

Wang, D., Clement, P., Smitz, J., & Derde, M. P. (1995). Concentrations of chemical mediators in nasal secretions after nasal allergen challenges in atopic patients. *European Archives of Oto-Rhino-Laryngology*(252 (Suppl 1)).

Wang, D. H., Tang, H. Q., Ling, Y. X., Fu, X., Han, H. Y. & Li, Y. Z. (2000). Observation of recent desensitized nose drops to treat allergic rhinitis [Tuimin dibiye zhiliao guominxing biyan de jinqi liaoxiao guancha]. *Journal of Hunan College of TCM [Hunan Zhongyi Xueyuan Xuebao], 20*(1), 43-45.

Wang, D. Y., & Clement, P. (2000). Pathogenic mechanisms underlying the clinical symptoms of allergic rhinitis. *American Journal of Rhinology, 14*(5), 325-333.

Wang, S., Tang, Q., Qian, W., & Fan, Y. (2012). Meta-analysis of clinical trials on traditional Chinese herbal medicine for treatment of persistent allergic rhinitis. *Allergy, 67*(5), 583-592.

Wang, Z. J., Tabakoff, B., Levinson, S. R., & Heinbockel, T. (2015). Inhibition of Nav1.7 channels by methyl eugenol as a mechanism underlying its antinociceptive and anaesthetic actions. *Acta Pharmacologica Sinca, 36*(7), 791-799.

West, S. L., Gartlehner, G., Mansfield, A. J., , , Poole. C., Tant, E., Lenfestey, N., . . . Lohr, K. N. (2010). *Comparative effectiveness review methods: Clinical heterogeneity*. (AHRQ Publication No. 10-EHC070-EF). U.S. Department of Health and Human Services. Retrieved from http://effectivehealthcare.ahrq.gov/. Accessed Mar 2016.

Westman, M., Lupinek, C., Bousquet, J., Andersson, N., Pahr, S., Baar, A., . . . Wickman, M. (2014). Early childhood IgE reactivity to pathogenesis-related class 10 proteins predicts allergic rhinitis in adolescence. *Journal of Allergy and Clinical Immunology*.

WHO. (1999). *WHO monographs on selected medicinal plants* (Vol. 1). Geneva, Switzerland.

WHO. (2009). *WHO monographs on selected medicinal plants* (Vol. 4). Geneva, Switzerland.

WHO. (2013). *WHO traditional medicine strategy: 2014-2023* Q. Zhang (Ed.) (pp. 76). Retrieved from http://www.who.int/medicines/publications/traditional/trm_strategy14_23/en/ . Accessed May 2016.

Winther, L., Malling, H. J., & Mosbech, H. (2000). Allergen-specific immunotherapy in birch- and grass-pollen-allergic rhinitis. II. Side-effects. *Allergy, 55*(9), 827-835.

Wiseman, N., & Ellis, A. T. (1996). *Fundamentals of Chinese Medicine [Zhong Yi Xue Ji Chu]*. Brookline, Massachusetts: Paradigm Publications.

Woerly, G., Honda, K., Loyens, M., Papin, J.-P., Auwerx, J., Staels, B., . . . Dombrowicz, D. (2003). Peroxisome proliferator–activated receptors α and γ down-regulate allergic inflammation and eosinophil activation. *The Journal of Experimental Medicine, 198*(3), 411-421.

Wong, G. W. K., Leung, T. F., & Ko, F. W. S. (2013). Changing prevalence of allergic diseases in the Asia-Pacific region. *Allergy, Asthma & Immunology Research, 5*(5), 251-257.

Wood, J. N., Boorman, J. P., Okuse, K., & Baker, M. D. (2004). Voltage-gated sodium channels and pain pathways. *Journal of Neurobiology, 61*(1), 55-71.

Wu, J. P., Wan, Y., Xie, Z. S. & Cao, S., H. (2012). The clinical effects of Loratadine tablets with Xinqin Keli on treating allergic rhinitis [Qileitatin quhe xinqin keli zhiliao guominxing biyan de liaoxiao]. *Seek Medical and Ask the Medicine [Qiuyi wenyao], 10*(10), 379.

Wu, M., Zhang, J. Y., Zhang, X., Ni, J. X., Lu, W. W., Ding, L. F., & Li, Z. (2009). Clinical observation of Flos magnoliae volatile oil nano-liposome nasal drops in treating paediatric allergic rhinitis [Xinyi huifayou nami zhizhiti dibiji zhiliao ertong bianyingxing biyan de linchuang guancha]. *Chinese Journal of Integrated Traditional and Western Medicine [Zhongguo Zhongxiyi Jiehe Zazhi], 29*(8), 740-742.

Xiao, L. & Rao, X. H. (2015). Clinical efficacy of acupuncture combined with treatment of Chinese herb for allergic rhinitis [Zhenyao jiehe zhiliao guomin biyan de linchuang guancha]. *Journal of Zhejiang Chinese Medical University [Zhejiang Zhongyiyao Daxue Xuebao], 29*(10), 762-763.

Xie, W. & Zhang, H. Z. (2009). Chinese herbs combined with radiofrequency treatment of allergic rhinitis analysis [Zhongyao lianhe denglizi shepin zhiliao bianyingxing biyan liaoxiao fenxi]. *Shandong Medical Journal [Shandong Yi Yao], 49*(48), 66-77.

Xin, Y. J., & Li, C. F. (2005). A clinical observation on the therapeutic effects of treating method with Qi-boosting, Yang-warming and blood-quickening on perennial allergic rhinitis [Yiqiwenyanghuoxuefa zhiliao changnianxing bianyingxing biyan de liaoxiao guancha]. *Chinese Journal of Otorhinolaryngology of Integrated Traditional and Western Medicine [Zhongguo Zhongxiyi Jiehe Erbiyanhouke Zazhi], 13*(2), 76-78.

Xiong, D. J., & Liu, P. (2013). *Chinese medicine otorhinolargngology [Zhongyi Eryanhou Kexue]* (3rd ed.). Beijing, China: China Traditional Chinese Medicine Publisher [Zhongguo Zhongyiyao Chubanse].

Xiong, T. Q., Qin, X. H., & Shen, Y.-J. (2006). Effects and mechanism of VOMbp on allergic rhinitis guinea pigs. *Pharmacology and Clinics of Chinese Materia Medica, 22*(02), 24-26.

Xu, Y. Y., Liu, X., Dai, L. B., & Zhou, S. H. (2012). Effect of Tong Qiao drops on the expression of eotaxin, IL-13 in the nasal mucosa of rats with allergic rhinitis. *Journal of the Chinese Medical Association : JCMA, 75*(10), 524-529.

Xue, C. C. L., Thien, F. C., Zhang, J. J., Da Costa, C., & Li, C. G. (2003). Treatment for seasonal allergic rhinitis by Chinese herbal medicine: A randomized placebo controlled trial. *Alternative Therapies in Health and Medicine, 9*(5), 80-87.

Xue, C. C., Thien, F. C., Zhang, J. J., Yang, W., Da Costa, C., & Li, C. G. (2003). Effect of adding a Chinese herbal preparation to acupuncture for seasonal allergic rhinitis: Randomised double-blind controlled trial. *Hong Kong Medical Journal, 9*(6), 427-434.

Xue, C. C. L., Zhang, A. L., Lin, V., Da Costa, C., & Story, D. F. (2007). Complementary and alternative medicine use in Australia: A national population-based survey. *Journal of Alternative & Complementary Medicine, 13*(6), 643-650.

Yan, X. L. (2011). Allergic rhinitis treated with modified Yupingfengsan in 115 cases [Yupingfengsan jiawei zhiliao bianyingxing biyan 115 li linchuang guancha]. *Journal of Beijing University of Traditional Chinese Medicine [Beijing Zhongyiyao Daxue Xuebao], 34*(5), 358-360.

Yang, S. H., Hong, C. Y., & Yu, C. L. (2002). The stimulatory effects of nasal discharge from patients with perennial allergic rhinitis on normal human neutrophils are normalized after treatment with a new mixed formula of Chinese herbs. *International immunopharmacology, 2*(12), 1627-1639.

Yang, S. H., & Yu, C. L. (2008). Antiinflammatory effects of Bu-zhong-yi-qi-tang in patients with perennial allergic rhinitis. *Journal of Ethnopharmacology, 115*(1), 104-109.

Yang, S. H., Yu, C. L., Chen, Y. L., & Chiao, S. L. (2010). Traditional Chinese medicine , Xin-yi-san, reduces nasal symtpoms of patients with perennial allergic rhinitis by its diverse immunomodulatory effects. *International Immunopharmacology, 10*(10), 951-958.

Yang, Z. C. (2004). *Allergic rhinitis observation on the effect of particle therapy of Xinqin [Zhongyao xinqin keli zhiliao bianyingxing biyan liaoxiao guancha]* Paper presented at the Chinese Medical Association Eleventh National Symposium on Traditional Chinese Medicine ENT [Zhonghua Zhongyiyao Xuehui Quanguo Dishiyijie Zhongyi Erbihouke Xueshuyan Taohui], Chengdu, China.

Yao, Z. X. (2006). *[Hepatotoxicity cocklebur and combination attenuated mechanism]*. (Masters), Heilongjiang University of Chinese Medicine, Heilongjiang, China.

Yazid, S., Sinniah, A., Solito, E., Calder, V., & Flower, R. J. (2013). Anti-allergic cromones inhibit histamine and eicosanoid release from activated human and murine mast cells by releasing Annexin A1. *PLoS One, 8*(3), e58963.

Ye, J. L., & Lin, J. Z. (2015). Guizhitang combined with mahuangfuzixixin decoction for treatment of 32 cases of allergic rhinitis [Xixin tang jiajian zhiliao guominxing biyan 32 li]. *Fujian Journal of Traditional Chinese Medicine, 46*(2), 46-47.

Ye, L., Li, J. S., Li, T. L., Jiang, X. Y., Tan, C., & Wang, D. J. (2016). Clinical observation of Liu's infantile tuina therapy for allergic rhinitis. *Journal of Acupuncture and Tuina Science, 14*(3), 202-206.

Yu, J., Song, M. Z., Wang, J., Li, Y. F., Lin, P., Que, L., & Bao, Z. (2013). In vitro cytotoxicity and in vivo acute and chronic toxicity of Xanthii Fructus and Its processed product. *BioMed Research International, 2013*, 12.

Zhang, C. S., Yang, A. W., Zhang, A. L., Fu, W. B., Thien, F. C. K., Lewith, G., & Xue, C. C. (2010). Ear-acupressure for allergic rhinitis: A systematic review. *Clinical Otolaryngology, 35*(1), 6-12.

Zhang, L., Han, D., Huang, D., Wu, Y., Dong, Z., Xu, G., . . . Bachert, C. (2009). Prevalence of self-reported allergic rhinitis in eleven major cities in China. *International Archives of Allergy and Immunology, 149*(1), 47-57.

Zhang, H. (2004). Treatment of perennial allergic rhintis 60 cases by Bimin decoction. *Journal of Traditional Chinese Medicine, 45*, 41-42.

Zhang, H. Z., Ren, S. X., Tang, Y. H., Wang, W. & Ye, J. P. (1996). Clinical observation of efficacy of immunotherapy combined with rhinitis nasal irrigation for perennial allergic rhinitis [Mianyi liaofa hebing biyan chongji zhiliao changnianxing bianyingxing biyan liaoxiao guancha]. *Chinese Journal of Otorhinolaryngology of Integrated Traditional and Western Medicine [Zhongguo Zhongxiyi Jiehe Erbiyanhouke Zazhi], 4*(2), 69-71.

Zhang, Y. (2007). 103 cases pf perennial allergic rhinitis health mixture treatment efficacy [Jianbiheji zhiliao changnianxing bianyingxing biyan 103 li liaoxiao guancha]. *Chinese Journal of Information on Traditional Chinese Medicine [Zhongguo Zhongyiyao Xinxi Zazhi], 14*(7), 58-59.

Zhao, B., Yang, X. B., Yang, X. W., & Liu, J. X. (2012). Biotransformation of prim-O-glucosylcimifugin by human intestinal flora and its inhibition on NO production and DPPH free radical. *Journal of Asian Natural Products Research, 14*(9), 886-896.

Zhao, Y. (2012). The curative effect of Tongqiaobiyankeli on allergic rhinitis [Tongqiaobiyankeli zhiliao guominxing biyan de liaoxiao guancha]. *Contemporary Medicine [Dangdai Zhongyi], 18*(295), 136-137.

Zhao, Y., Woo, K. S., van Hansselt, C. A., Wong, K. W., Cheng, K. F., Lam, C. W. K. & Leung, P. C. (2009). Treatment of perennial allergic rhinitis using Shi-Bi-Lin, a Chinese herbal formula. *Journal of Ethnopharmacology, 122*, 100-105.

Zhao, Z. Z., Liang, Z. T., Jiang, Z. H., Leung, K. S. Y., Chan, C. L., Chan, H. Y., . . . Law, K. W. (2008). Comparative study on the aristolochic acid I content of *Herba Asari* for safe use. *Phytomedicine, 15*(9), 741-748.

Zheng, J., & Luo, H. Y. (2007). *Clinical observation of the effect of Chinese traditional medicine Xingbiningjiaoji in children allergic rhinitis [Zhongyao xingbi ningjiaoji zhiliao xiao'er bianyingxing biyan linchuang liaoxiao guancha]*. (Masters), Fujian College of Traditional Chinese Medicine, Fujian, China.

Zhong, R. Q. (2013). *Clinical study carminative Tongqiao soup treatment of perennial allergic rhinitis.* (Masters), Beijing University of Chinese Medicine, Beijing, China.

Zhou, P. M., Zhang, Z. H., He, G., Wang, X., Yin, M., Chen, W., . . . Du, P. (2001). Clinical observation of 93 cases of allergic rhinitis using Xinzhi naristillae [Xinzhi dibiji zhiliao bianyingxing biyan 93 li linchuang guancha]. *Chinese Journal of Traditional Medical Science and Technology [Zhongguo Zhongyiyao Keji], 8*(4), 254-255.

Zhou, S. J. & Xie, Y. M. (2005). Clinical observation of integrative medicine in treatment of allergic rhinitis [Zhongxiyi jiehe zhiliao bianyingxing biyan liaoxiao guancha]. *Journal of Guangdong College of Pharmacy [Guangdong Yaoxueyuan Xuebao], 21*(3), 372-373.

Zou, W. Q., Niu, Q. Y., Liu, X. R., & Xing, W. D. (2012). 52 clinically deficient cases of allergic rhinitis utlising desensitisation therapy of Tuomintongqiao capsules [Tuomintongqiao jiaonang zhiliao qixuxing guominxing biyan 52 li linchuang guancha]. *Yunnan Chinese Medicine Journal [Yunnan Zhongyiyao Zhazhi], 33*(6), 36-37.